An Investigation of Eating Disorder Neurocognitive and Behavioural Endophenotypes in Twins

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Abstract

Background: Cognitive styles, emotional processing and behavioural traits are involved in the aetiology and maintenance of eating disorders. Some of these traits are present post recovery and in first-degree relatives suggesting that they may be endophenotypes.

Aims: The aim of this study was to examine cognitive styles, emotional processing and behavioural traits in female twins with eating disorders in order to explore their genetic basis. Such investigations will increase our knowledge of the aetiological architecture that underlies eating disorders.

Methods: In a sample of twins representative of the population (n=3338), the heritability of psychological symptoms thought to be related to eating disorders was estimated using structural equation modelling of questionnaire data. In a more in-depth face-to-face study, a smaller group of 114 clinical and control twins (n=53 met lifetime DSM-IV eating disorder criteria, n=19 non-eating disorder cotwins and n=42 controls) were assessed using a semi-structured interview and an objective assessment of cognitive styles, emotional processing and behavioural traits. To explore the heritability of these, within–pair-correlations were calculated and generalised estimating equations compared probands with non-eating disorder cotwins and controls.

Results: In the population sample, the psychological symptoms related to eating disorders were found to be moderately heritable. In the clinical sample of twins, there appeared a genetic basis to the life course of the eating disorder. Childhood traits reflecting an obsessive compulsive personality and lifetime impulsive behaviours were found to be familial traits. Analysis of cognitive styles indicated they had a genetic and familial basis and emotional processing also showed a genetic and familial basis at trend level. There was some evidence of altered reward sensitivity in people with bulimic disorders, although less evidence of a substantial genetic basis.

Conclusions: Psychological symptoms related to eating disorders were moderately heritable in the population twin sample. The clinical studies were exploratory, in part due to the limited sample size. Some elements of the findings lent support to cognitive and emotional processing traits being endophenotypes for eating disorders. However the relatively small sized differences between clinical and control samples as well as the differences between age groups and across the diagnostic spectrum, demonstrates that these particular measures may be restricted in their ability to inform the future diagnosis and taxonomy of eating disorders. Future studies with larger samples are required to confirm the present study's findings.

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The student was awarded a Medical Research Council PhD Scholarship. This in part funded the research presented throughout this thesis.

Common Abbreviations Used Throughout the Thesis

AN = anorexia nervosa

ANR = restrictive anorexia nervosa

ANBP = anorexia nervosa binge purge subtype

APA=American Psychiatric Association

BMI = body mass index

BD= bulimic disorders (bulimia nervosa or binge eating disorder)

BED = binge eating disorder

BN = bulimia nervosa

D = cohens d effect size

DASS = depression stress and anxiety scale (21 item version)

DERS = difficulties in emotion regulation scale

DSM = Diagnostic and Statistical Manual

DZ = dizygotic

ED(s) = eating disorder(s)

EDNOS = eating disorder not otherwise specified

Estroop = pictorial emotional stroop task

GEFT=group embedded figures task

C = healthy controls

IQ = intelligence quotient

MZ = monozygotic

NART= national adult reading test

Non-ED cotwin(s) = unaffected twin sibling(s)

Non-AN cotwin(s)= unaffected twin sibling(s) whose proband has anorexia nervosa

Non-BD cotwin(s)= unaffected twin sibling(s) whose proband has a bulimic disorder

OCPD = obsessive compulsive personality disorder

OCP = obsessive compulsive personality

OCD = obsessive compulsive disorder

OCI-R = obsessive compulsive inventory - revised

ROCF = rey osterrieth complex figure task

RME = reading the mind in the eyes task

SD = standard deviation

WCST = wisconsin card sort task

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Thesis Outline

The aim of this thesis is to achieve a greater understanding of the causes of cognitive, emotional and behavioural profiles that are found in eating disorders. A review of the current literature has indicated that various traits are potential risk markers for eating disorders (EDs) with some being present post recovery and in their unaffected first degree relatives, suggesting that they may be heritable risk factors. Overall, this thesis aims to take the next step by utilising twin methodology to investigate the extent that these traits pose a genetic risk.

To embark upon this investigation, the heritability of self reported psychopathological eating disorder features will be investigated in a large sample of female twins that are representative of the general population (n=3338). This justifies the subsequent in-depth studies of twins with clinically defined eating disorders (n=53 met lifetime DSM-IV eating disorder criteria, n=19 non-eating disorder cotwins and n=42 controls) designed to explore the genetic basis of cognitive, emotional and behavioural profiles associated with the condition. Comparing the pattern of risk between identical and non-identical twins provides a natural experiment to parse out the effects of genes on these traits. This thesis employs the criteria outlined by Gottesman and Gould (2003) to investigate whether these may be considered as endophenotypes of eating disorders. Specifically the heritability, the familial risk and the association with eating disorders are examined. The use of valid and practical measures allows this assessment to be transferable to treatment settings, which can assist clinicians in their diagnosis and knowledge of risk factors.

As such seven empirical studies were conducted (outlined in the following). On the basis of previous research it is hypothesised that there will be a genetic component to the traits and behaviours under investigation

Chapter 2 (Study 1):

This chapter explores the heritability of three subscales included in the Eating Disorder Inventory (Garner et al 1991) - 1) body dissatisfaction, 2) drive for thinness and 3) bulimia, in a large representative sample of twins recruited through the UK twin registry. Biometric model fitting is used to provide estimates of the genetic and environmental contributions to these traits.

Chapter 4 (Study 2):

This chapter explores how eating disorder symptoms co-aggregate within identical and non-identical twin pairs across the life course with the aim of exploring the heritability of eating disorders and its prognosis.

Chapter 5 (Study 3):

This chapter explores the familial and genetic basis of childhood obsessive compulsive personality traits measured by the EATATE semi structured interview (Anderluh et al 2003) in a twin sample with eating disorders and a comparative sample of singletons.

Chapter 6 (Study 4):

This chapter explores the familial risk and genetic basis of lifetime impulsive behaviours (i.e. alcohol abuse, self harm or gambling) measured by the EATATE semi structured interview (Anderluh et al 2003) in a twin sample with eating disorders and a comparative sample of control singletons.

Chapter 7 (Study 5):

This chapter explores the familial risk and genetic basis of neurocognitive traits including set shifting and central coherence in a twin sample with eating disorders and a comparative sample of control twins.

Chapter 8 (Study 6):

This chapter explores the familial risk and genetic basis of emotional related traits including emotion recognition, social attentional biases and emotional regulation in a twin sample with eating disorders and a comparative sample of control twins.

Chapter 9 (Study 7):

This chapter explores the familial risk and genetic basis of reward sensitivity and motivation related behaviour in a twin sample with eating disorders and a comparative sample of control twins.

Disseminations Associated With This Thesis

•Kanakam, N. and Treasure, J. (accepted). A review of cognitive neuropsychiatry in the taxonomy of eating disorders: State, trait or genetic? *Cognitive Neuropsychiatry.*

- *This paper formed the basis of Chapter 1*

•Kanakam, N. and Treasure, J. (in preparation). Co-aggregation of eating disorders within identical and non-identical twin pairs with eating disorders.

- *This paper formed the basis of Chapter 4*

-Kanakam, N., Anderluh, M. and Treasure. (in preparation). Childhood obsessive compulsive personality traits in women with eating disorders: An investigation in twins.

- *This paper formed the basis of Chapter 5*

•Kanakam, N., Rauolt, C., Collier, D. and Treasure, J. (2012). Set shifting and central coherence as neurocognitive endophenotypes in eating disorders: A preliminary investigation in twins. *The World of Biological Psychiatry*

- *This paper formed the basis of Chapter 7*

•Kanakam, N., Krug, I., Collier, D. and Treasure, J. (submitted). Emotional processing as a behavioural endophenotype in eating disorders: A preliminary investigation in twins.

- *This paper formed the basis of Chapter 8*

Conference Presentations Associated With This thesis

•Kanakam, N. and Treasure, J. (2010). Emotional Processing as a Behavioural Intermediate Phenotype in Eating Disorders: A Preliminary Investigation in Twins. Division of Clinical Psychology Annual Conference. Manchester

•Kanakam, N. and Treasure, J. (2011). Reward Sensitivity as an Intermediate Phenotype in Eating Disorders: A Preliminary Investigation in Twins. BABCP conference. Surrey.

In addition to these conferences, data from this thesis has been presented at smaller research meetings:

• In-house research meetings at the Institute of Psychiatry, Kings College London, chaired by Prof Ulrike Schmidt, Prof Janet Treasure and Dr Kate Tchanturia.

• At a biannual Neuro Network research meeting at Great Ormond Street Hospital, London.

Declaration of Candidate's Role in Each of the Studies

Chapter 1 – Introduction:

The candidate conducted an in depth literature review using systematic review techniques.

Chapter 2 - Study Investigating the Heritability of Psychological Symptoms Associated With Eating Disorders in a Representative Sample:

The candidate collaborated in the design of this study which was led by Professor Collier. The candidate analysed and interpreted the data pertaining to the present study. Two other researchers who were formally trained in the relevant statistical procedures confirmed that these were performed correctly.

Chapter 4 - Study Investigating Eating Disorders Across the Life Course in Twins With Eating Disorders:

The candidate recruited the twin sample and administered all of the eating disorder diagnostic interviews. The final diagnosis was confirmed between the candidate and collaboration with two other clinicians. The candidate designed the study, analysed and interpreted the data within the current evidence base. All the statistical analysis was confirmed as being the most appropriate procedure by a statistician.

Chapters 5 and 6 - Studies Investigating the Familial and Genetic Basis of Obsessive Compulsive Personality Features and Impulsive Behaviours in Twins With Eating Disorders:

The candidate analysed and interpreted the data pertaining to obsessive compulsive personality traits and impulsive behaviours, within the context of previous research. Data for the controls singletons was obtained with permission from a previous published study conducted by Anderluh and colleagues (2003).

Chapter 7 - Study Investigating the Familial and Genetic Basis of Neuropsychological Traits in Twins With Eating Disorders:

The candidate designed the study. Along with a volunteer, the candidate carried out all of the assessments and data entry. The candidate scored, analysed and interpreted the data pertaining to neuropsychological traits within the context of previous research. A statistician verified that the statistical procedures were correct. Data for one monozygotic twin pair was

obtained with permission from previous published studies conducted by Roberts and colleagues (2010; submitted).

Chapters 8 and 9 - Studies Investigating the Familial and Genetic Basis of Behavioural Traits in Twins With Eating Disorders:

The candidate designed the study and along with a volunteer carried out the assessments and data entry for this study. The candidate scored, analysed and interpreted the data pertaining to behavioural traits within the context of previous research. A statistician reviewed and confirmed that the statistical procedures were performed correctly.

1. Chapter 1: Introduction

1.1. Introduction to the chapter

Eating disorders are psychiatric conditions, which impact severely on the individual's physical and psychological well-being (Keel, et al. 2003; Tiller et al. 1997; Wentz et al. 2009). Their aetiology is complex, involving a premorbid genetic predisposition that interacts with environmental factors such as socio-cultural and interpersonal factors (Collier and Treasure, 2004). The genetic basis of eating disorders is evident (Mazzeo et al. 2009; Bulik et al. 2006; Bulik et al. 2010; Javaras et al. 2008), although less is known about the genetic basis of more implicit traits such as thinking styles that may increase the risk of eating disorders.

The overall aim of this introduction is to describe the foundation of this thesis. This begins with outlining the current classification of eating disorders and its' difficulties. Proposals of how to address these difficulties are presented and the idea of investigating endophenotypes; traits that may be more closely associated with genes than the clinical symptoms, is introduced (Gottesman and Gould, 2003). The current evidence base of potential endophenotypes in eating disorders is presented. Specifically, evidence of obsessive compulsive personality traits, impulsive behaviours, difficulties in set shifting, weak central coherence, emotional processing difficulties and altered reward sensitivity is presented for people both in the acute and recovered phase of the illness as well as their first degree relatives. At present there is limited research linking these traits with an inherited biological vulnerability and this question forms the foundation of this thesis.

1.2. Eating disorder phenotypes

According to the Diagnostic and Statistical Manual of the American Psychiatric Society (DSM IV (4^{th} edition, APA, 2000) three broad diagnostic categories of eating disorders exist: Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Eating Disorders Not Otherwise Specified (EDNOS).

1.2.1. Anorexia nervosa

Anorexia Nervosa was first described by Gull in 1868. The current DSM classification includes the symptoms outlined in table 1.1.There are two subtypes of AN: restricting (AN-R) and the binge-purge type (AN-BP). The restricting subtype is characterised by behaviours of extreme and prolonged fasting and restraint. The binge purge subtype is also defined by restraint, punctuated by episodes of overeating followed by behaviours to compensate for weight gain such as self-induced vomiting, the misuse of laxatives, diuretics, enemas and exercise.

Table 1.1: Current diagnostic criterion for AN according DSM-IV (1994)

DSM-IV criteria for anorexia nervosa
A. Refusal to maintain a body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to the maintenance of body weight less than 85 per cent of that expected; or failure to make expected weight gain during a period of growing, leading to body weight less than 85 per cent of that expected) B. Intense fear of gaining weight or becoming fat, even though underweight C. Disturbance in the way that weight or shape is experienced, undue influence of body weight or shape on self-evaluation, denial of the seriousness of the current low body weight D. In postmenarcheal females, amenorrhoea, i.e. the absence of at least three consecutive menstrual cycles

1.2.2. Bulimia nervosa

Bulimia Nervosa was first described by Russell in 1979, as a variant of anorexia nervosa. The current DSM-IV classification includes the symptoms outlined in Table 1.2. There are two subtypes of BN: purging (BN-P) and the non-purging types (BN-NP). Both types are characterised by binge eating episodes accompanied by feelings of lack of control. The purging type involves compensatory behaviours such as self-induced vomiting or misuse of laxatives and diuretics to counteract the effects of overeating. The non-purging types may not include these purging behaviours although they may involve compensatory behaviours such as fasting or excessive exercise.

Table 1.2: Current diagnostic criterion for BN according DSM-IV (1994)

DSM-IV criteria for bulimia nervosa
Recurrent episodes of binge eating. An episode of binge eating is characterised by both of the following: 1) Eating, in a discrete period of time (e.g. within any two-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances 2) A sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating) B. Recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self induced vomiting; misuse of laxatives, diuretics, enemas or other medications, fasting or excessive exercise C. The binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for three months D. Self-evaluation is unduly influenced by body shape and weight E. The disturbance does not occur exclusively during episodes of anorexia nervosa

1.2.3. EDNOS

Eating disorders that do not meet the criteria for the aforementioned categories are classed as Eating Disorder Not Otherwise Specified. This category is the most prevalent of all the ED diagnoses (Thomas, Vartanian and Brownell, 2009). The EDNOS category is applied to individuals on the restrictive end of the ED spectrum who meet all the criteria for anorexia nervosa except amenorrhoea or despite significant weight loss the individual's weight is still in the normal range. At the other end of the spectrum, EDNOS is also applied to individuals with bulimic eating disorders such as those who meet all of the criteria for bulimia nervosa except that binge eating and inappropriate compensatory behaviours occur less than twice a week. A review of all studies conducted between 1987 and 2007 indicated that these cases do not differ significantly from full syndrome AN and BN cases and could be incorporated into existing DSM-IV categories (Thomas, Vartanian and Brownelll 2009). Binge eating disorder (BED) is another EDNOS category that is applied to individuals who engage in binge eating characteristic of BN but do not use inappropriate compensatory behaviours. BED is the only condition classified under EDNOS that will receive its own separate category as a distinct condition in the DSM-V to be delivered in 2013. Lastly, there are two EDNOS categories, which are not characterised by restrictive or lack of control eating behaviours and may be conceptualised as distinct categories. These include individuals who regularly use inappropriate compensatory behaviours after eating relatively small amounts of food and individuals who repeatedly chew and spit out normal amounts of food.

1.3. Epidemiology

The lifetime prevalence for DSM-IV defined anorexia nervosa, bulimia nervosa and binge eating disorder are 0.9%, 1.5%, and 3.5% respectively (Hudson et al 2007). The prevalence of these conditions in twins is of specific interest to the present thesis. In a representative sample of female twins aged 28-39, the lifetime prevalence of AN was 1.9%, with an additional 2.4% meeting similar criteria except amenorrhoea. The lifetime prevalence of BN was somewhat higher at 2.9% and this was also the case for BED (Wade et al 2006).

Anorexia nervosa mainly affects women, with 90% of cases being female (Fairburn and Harrison 2003). AN is more likely to be found in young women with the highest incidence rate in primary care being women aged 10 to 19 years (Van Hoeken et al 2003). The average lifetime prevalence of AN in young females is 0.3% (Hoek, 2006; Van Hoeken et al 2003). Similar to AN, the highest incidence of BN is in young females aged 10 to 19 years (Keel and Mitchell 1997). The average lifetime prevalence of BN in young females is 1% (Van Hoeken et al 2003).

There have been changes in the prevalence of bulimia nervosa over time possibly due to socio-cultural changes (explained in section 1.7)

1.4. Prognosis

A review of 119 studies of AN has indicated that on average, less than 50% recover and 20% remain chronically ill, with similar findings for BN (Steinhausen and Weber 2009; Steinhausen, 2002).

Others have concluded similarly, with four year remission rates being 57% in AN, 47% in BN and the most favourable being 82% in BED (Agras et al 2009). Keel and Browns' (2010) review of the course and outcome of eating disorders has concluded that there is a need for follow up studies of BED, with a period longer than 5 years.

In comparison to the general population, people with eating disorders have a higher risk of mortality. In bulimia nervosa the standardised mortality ratio is 1.3% (Keel, Dorer, Eddy, Franko, Charatan and Herzog, 2003). This ratio is even more elevated in AN, ranging between 6.2 and 10.5 % (Birmingham et al. 2005; Papadopoulos et al. 2009; Lowe et al. 2001). Longitudinal studies have found lower levels of the standardised mortality rate for AN at 3.7% after a 20 to 40 year follow up (van Hoeken Seidell and Wijbrand, 2003).

1.5. Chronic disability

Difficulties in diagnosis and their association with other psychopathology means these disorders are frequently under-treated and outcome is poor (Hudson et al 2007). Similarly, other studies have reported that only half of those with AN recover and approximately 6–10% develop a chronic condition (Berkman et al. 2007; Lowe et al. 2001).

Eating disorders have been placed 10th in terms of burden of disease (years of life lost through death or disability) in women aged 15-24 years (Mathers et al 1999). Education (Byford et al. 2007) and vocational functioning is disrupted (Hjern et al. 2006). Social isolation is common and up to 25% have poor psychosocial functioning (Tiller et al. 1997; Wentz et al. 2009). The costs of these disabilities are high (Su and Birmingham 2003).

1.6. Aetiology

A multi-factorial aetiology involving an interaction between genetic and environmental factors is considered a potent risk for eating disorders. An example of this includes biological factors such as altered serotonin function or cognitive and personality traits interacting with environmental factors such as parenting styles or life events (Collier and Treasure, 2004).

There have been numerous reviews of environmental risk factors for eating disorders. Noteworthy are those reviewing studies which adopted longitudinal and cross-sectional designs. These have found that common risk factors include 'gender, ethnicity, early childhood eating problems, elevated weight and shape concerns, negative self-evaluation, sexual abuse and other adverse experiences and general psychiatric morbidity' (Jacobi et al 2004). A longitudinal

cohort study over a period of 3 years which assessed 236 control women of college age found critical comments about eating from teachers of siblings and a history of depression were the greatest risk factors for this group (Jacobi et al 2011). Other reviews have found perceived pressure for thinness, thin-ideal internalisation and negative affect to be strong risk factors for eating disorders (Stice et al 2010). There is support for this from an 8 year prospective study of 496 adolescent girls which found that depression amplifies the risk that body dissatisfaction poses to the development of eating disorders (Stice et al 2011).

1.6.1. Models of aetiology

The following sections outline four different models that explain how eating disorders may be caused and maintained. The models are informed by social, cognitive and biological theories. They provide a framework in which this thesis is set and suggest testable hypotheses.

1.6.2. Cognitive-interpersonal maintenance model of AN (Schmidt and Treasure, 2006)

The 'cognitive interpersonal model of anorexia nervosa' transcends its' counterparts with it's main focus on maintaining factors outside of weight or shape concerns (Schmidt and Treasure, 2006).This model may be seen to consist of two main parts. The first relates to antecedent risk factors such as the cognitive styles of perfectionism and cognitive rigidity and the emotional style of avoidance. The second area considers the environmental factors that develop as a consequence of the disorder and those that maintain the symptoms such as the response of close others. On their own some of these factors are not specific to AN, however when combined these explain the symptoms associated with AN. The factors are explained in the following:

1.6.2.1. Cognitive style

The cognitive style characteristic of AN is postulated to be a vulnerability factor predating its onset (Schmidt and Treasure, 2006). This style encompasses obsessive compulsive personality traits, particularly perfectionism and rule bound behaviours. It may manifest in childhood and later expresses itself in clinical symptoms such as strict dietary rules or behaviours such as difficulty adapting to change and a fear of making mistakes. Extreme weight loss can exacerbate rigid thinking and act to maintain its symptoms (Schmidt and Treasure, 2006).

1.6.2.2. Emotional style

Pervasive cognitive, behavioural and emotional avoidance - in particular pulling away from close interpersonal relationships, often predates onset suggesting that they are risk factors (Schmidt and Treasure, 2006). Research has indicated that people with AN have significantly higher levels of social avoidance (measured by the Social Avoidance and Distress scale; Watson and Friend, 1969) and social phobia (measured by the Social Phobia Scale; Liebowitz, 1987). Furthermore a diagnosis of social phobia predates the onset of AN in 65 % of cases, suggesting that these difficulties are a risk factor to eating disorders (Flament and Godart, 1995). Women

with eating disorders (AN and BN) experience greater levels of loneliness, shyness and inferiority in adolescence (aged 11 to 17) although there appear to be no differences between eating disorders and controls in childhood (below age 10) (Troop and Bifulco, 2002).

1.6.2.3. Pro-anorexic thinking

Schmidt and Treasure (2006) propose that the individual may hold beliefs that the disorder serves a positive or adaptive function, which is specific to their intrinsic temperamental vulnerability traits. The beliefs can arise intra-personally, when the individual becomes aware that adhering to strict rules of diet and exercise creates a sense of safety from the fear of others, thereby enabling emotional avoidance (Schmidt and Treasure, 2006).

1.6.2.4. Interpersonal

Other people's responses to the symptoms such as criticism, hostility or emotional over involvement influences the outcome and maintenance of anorexia nervosa (Schmidt and Treasure, 2006). In such environments where there is high levels of expressed emotion, AN can have a positive function for the individual whereby close others respond to the symptoms with comfort and reassurance. The obvious physical symptom of extreme weight loss sends a clear message to close others of the distress felt by the individual. This mutually reinforces the pro-anorexic beliefs in a cycle whereby anorexia nervosa is maintained in order to elicit support and care. Conversely, the overt symptoms of AN can create an interpersonal struggle for control within families, resulting in criticism and dominance. This can result in the individual avoiding difficult interactions, which only reinforce the need to maintain the disordered behaviours (Schmidt and Treasure, 2006).

The cognitive interpersonal model of AN (Schmidt and Treasure 2006) proposes that these cognitive and emotional styles are present prior to onset suggesting that they are stable traits which foster vulnerability. Investigation of the genetic basis of these styles could assist in demonstrating their endophenotype status. These questions provide testable hypotheses to be addressed by this thesis. Other factors such as pro-AN thinking and interpersonal factors arise from the environment and have active roles in maintaining the disorder (Schmidt and Treasure, 2006).

1.6.3. A theoretical model of eating disorders (Treasure, in progress)

Treasure (in progress) has outlined a biological explanation for the anomalies in emotional processing and reward sensitivity associated with eating disorders by drawing on a model proposed by Kaye (et al 2009) which explains eating behaviour in AN. Kaye, et al (2009) proposed that in AN, there is an imbalance between top down processes or cognitive control and bottom up homeostatic and hedonic processes. This imbalance may be due to altered serotonin and dopamine metabolism. In such cases, excessive cognitive control occurs to maintain a healthy milieu. Treasure (in progress) has expanded on this, by applying these

processes trans-diagnostically and to non-eating related symptoms. It is argued that this imbalance also explains more general anomalies in mood, emotion regulation, reward sensitivity, interoceptive functioning and social cognition. It is unclear whether these anomalies are primary or secondary consequences of the disorder. However, it is clear that these traits are maintaining factors, which make it difficult to recover. After onset, the imbalance between these systems is increasingly altered as a consequence of the physical symptoms associated with eating disorders. This additionally moderates prognosis and outcome. In comparison to Treasure and Schmidt (2006), this model has incorporated reward sensitivity to explain eating disorders. The factors accounted for in this model are outlined in the following:

1.6.3.1. Cognitive styles

This model (Treasure, in progress) proposes that those with eating disorders have marked deficits in cognitive flexibility (Roberts et al 2007; Tchanturia et al 2011a; Abbate-Daga et al 2011; Konstantakopoulos et al 2011; McAnarney et 2010; Roberts et al 2010, Teconi et al 2010; Nakazato et al 2010; Nakazato et al 2008) although these partly attenuate with recovery (Tenconi et al 2010; Nakazato et al 2008; Nakazato et al 2008; Tchanturia, Morris, Anderluh, Collier, Nikolaou, Treasure,2004; Tchanturia et al 2011a). An environmental event may trigger the person into applying cognitive control to eating. In addition, a detail focused information processing style is present in the illness state and after recovery. It is argued that these may be antecedent risk factors although exacerbated in the illness state by the physical symptoms.

1.6.3.2. Emotional regulation and social functioning

Eating Disorders have difficulties in emotional regulation and inferring emotional states in others (Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c; Oldershaw et al., 2010) resulting in high levels of anxiety and interpersonal difficulties (Zucker et al 2007: Godart et al 2000; Kaye et al 2004). During the acute phase, reward from social stimuli continues to be reduced causing the individual to become entrenched in their ED and increasingly isolated. There is research (Harrison et al 2010c; Cardi et al, 2012) to suggest that some difficulties perpetuate the illness and persist well into recovery. However the current evidence base is limited and it remains unclear whether these are state or trait related features (Treasure, in progress).

1.6.3.3. Reward

A systematic review of reward processes in EDs has determined that there is increased sensitivity to punishment and decreased sensitivity to reward [measured by the Temperament and Character Inventory; (Cloninger et al., 1993), Tridimensional Personality Questionnaire; (Cloninger, 1987) and BIS/BAS scale (Carver and White, 1994)] in all forms of eating disorders (Harrison et al. 2010a) and this may explain fearful behaviours (Treasure, in progress). Increased sensitivity to punishment is best explained by Gray's theory (1970) of brain and behaviour which proposes that there are two behavioural systems underling behaviour. The

Behavioural Inhibition System (BIS – the avoidance system) is reflected in personality dispositions reflecting anxiety, sensitivity to punishment, and non-reward (Carver and White, 1994). Whereas the Behavioural Activation System (BAS) is reflected in personalities that experience positive feelings when exposed to reward cues and is sensitive to reward and escape from punishment (Carver and White, 1994). Sensitivity to punishment (the BIS) appears to be most heightened in those with AN (Harrison et al 2010a). Specifically, disgust sensitivity may explain avoidance and shame associated with food. It is proposed that reward sensitivity not only acts as a maintaining factor but may also determine prognosis in terms of the duration of restriction and whether binge eating develops (Favarro et al 2005; Tozzi et al 2005).

1.6.3.4. Body awareness and interoceptive functioning

A reduced perception of bodily sensations resulting in difficulties determining satiety or hunger is present in the acute phase of an eating disorder (Treasure, in progress). Studies have shown that women with AN have significantly greater difficulties in their ability to discriminate sensations related to hunger and satiety (measured by the EDI interoceptive scale) and difficulties accurately perceiving physical body signals measured by a heartbeat perception task (Pollatos et al 2008). Another study of women with AN and BN has demonstrated that these difficulties are transdiagnostic and a significant predictor of clinical severity (Eshkevari et al 2011). Studies which have examined interoceptive difficulties when anticipating a meal of high-calorie foods have found hypoactivity to occur in the hypothalamus, amygdala and anterior insula in women with AN and those who were weight-restored (Holsen et al 2011). These interoceptive difficulties extend to pain sensitivity, taste, tactile and perception. However, again it is unclear whether these are state related or traits.

1.6.3.5. Brain structure

In AN there are abnormalities in brain structure with some parts being atrophied during the acute state (Suchan et al. 2011; Joos et al. 2010; Gaudio et al. 2011). Some of these resolve after recovery, (Wagner et al. 2006; Muhlau et al. 2007; Castro-Fornieles et al. 2009) however further research is needed to reach a clear conclusion.

1.6.3.6. Brain function

The structural and metabolic changes which occur in the brain during the acute phase of eating disorders influence brain function. FMRI (functional magnetic resonance imaging) has been a primary technique to assess brain function, in conjunction with tasks that elicit brain activation in areas thought to be specific to eating disorder symptoms (Frank and Kaye, 2012). These include responses to food, taste and body perception. One study which presented images of food and aversive (non-food) stimuli to individuals ill with AN and BN, found a medial prefrontal brain response to symptom-provoking stimuli in both conditions, supporting the transdiagnostic perspective of eating disorders (Uher et al 2004). Furthermore greater activation in the medial prefrontal cortex and anterior cingulate cortex (ACC) persists in those recovered from AN

(having maintained a normal weight for 2 years) as well as those with chronic AN (illness duration mean: 12.5 yrs, s.d: 3.6) suggesting that it may be a trait feature. These areas of the brain are typically involved in decision making and reward expectancy. The findings indicate that the prefrontal cortex is involved in anxiety activation and decision making which underlies food restriction (Uher et al 2003).

In addition there are anomalies in brain activation that occur when ingesting food, which persists in those recovered. A study of those recovered from AN-R found decreased neural activation in the insula, including the primary cortical taste region after ingesting a solution of sucrose diluted in water (Wagner et al 2008). Whereas in those recovered from BN, there is decreased activation in the ACC which is typically involved in error monitoring and reward expectancy (Frank et al 2006).

Altered brain function may also be accountable for distorted body perception in eating disorders. In females with AN there is increased activation in the intraparietal lobule (which is involved in visuo-spatial processing) when presented with digitally distorted images of their own body (Wager et al 2003). In both AN and BN, there is reduced lateral fusiform gyrus activation in response to line drawings of body shapes that are either, under or overweight and normal weight. This brain response may be due to their comparatively higher levels of aversion, seen in response to body images (Uher et al 2005).

A comprehensive review of brain function in eating disorders is beyond the aims of this chapter. Nevertheless it is clear that anomalies in brain activation occur, some of which are common to both AN and BN and could pose as a potential risk to developing an eating disorder. One hypothesis which has attempted to combine empirical evidence of brain function in AN has proposed a rate limiting dysfunction in the insular cortex (Nunn, Frampton, Gordon Lask, 2008). This structure is thought to have dense connections with other parts of the brain. The insular cortex integrates the neural circuitry of the frontal, somatosensory, parietal cortices and subcortical structures including the amygdala, hippocampus, hypothalamus and striatum. There is evidence that these structures are involved in emotional and reward processing, body size evaluation, obsessive compulsive behaviours, anxiety and executive function. The insular cortex is also thought to mediate the balance between adapting to the environment and regulating internal homeostasis (Nunn et al, 2008). This hypothesis (Nunn et al, 2008) has not yet been expanded to explain BN. Furthermore, dysfunction of the insular cortex may not specific to eating disorders since it is also common to mood disorders, panic disorders, PTSD, obsessive-compulsive disorders and schizophrenia (Nagai, Kishi and Kato, 2008).

Treasure's model (in progress) of eating disorders proposes that dysregulated homeostatic and hedonic processes causes excessive cognitive control. This imbalance contributes to an array of symptoms seen in eating disorders. It is similar to the 'cognitive interpersonal model of AN'

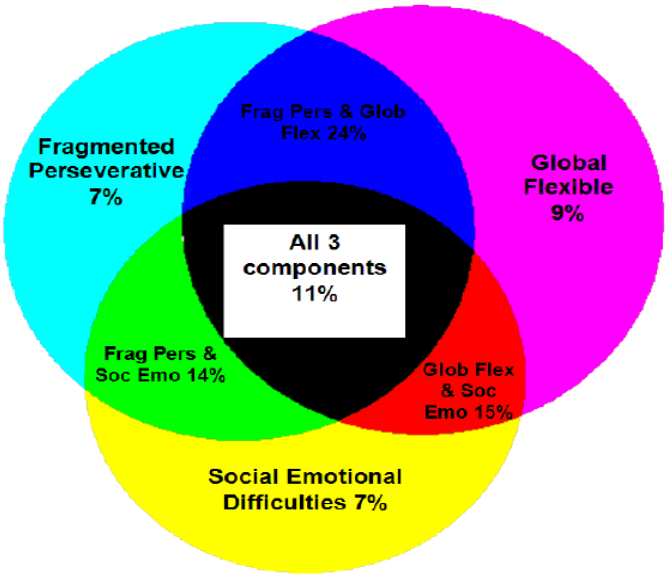
(Schmidt and Treasure 2006) in proposing that cognitive and emotional styles are risk factors that are exacerbated in the illness state. However, Treasure's model (in progress) extends this to provide a transdiagnostic model of eating disorders that accounts for altered reward sensitivity. This factor differs across the eating disorder spectrum and may predict prognosis in terms of the development of binge eating. The question of whether altered reward sensitivity differs across the eating disorder spectrum and predicts prognosis will be investigated in this thesis.

1.6.4. Harrisons model (2010)

Harrison (2010) has investigated the model proposed by Treasure and Schmidt (2006) to find out how cognitive styles such as rigidity, detail focused processing and difficulties in emotional functioning are related to eating disorders and their long term outcome. Using principal components analysis, it was revealed that within eating disorders there exists 3 independent profiles; the 'fragmented perseverative', 'global flexible' and 'social emotional difficulties'. The 'fragmented perseverative' profile refers to weak central coherence [measured by the Group Embedded Figures Task, (Witkin, Oltman, Raskin, and Karp, 2002) and Rey Osterrieth Complex Figure Task, (Osterrieth 1944)] and inefficiencies in set shifting [measured by the Brixton task (Burgess & Shallice, 1997) and the Wisconsin Card Sorting Test, (Heaton et al., 1993)]. The 'global flexible' profile is the antonym of the fragmented perseverative' style. Lastly the 'social emotional difficulties' profile refers to emotional processing difficulties [measured by the Reading the Mind in the Eyes paradigm (Baron-Cohen et al 1997) and the Pictorial Emotional Stroop task (Ashwin et al 2006)].

Those currently with an eating disorder or recovered were found to have higher scores for the 'fragmented perseverative style' and 'social emotional difficulties' and lower scores for the 'global flexible style' in comparison to controls. Whilst these 3 styles were not indicative of a diagnostic group they were found to significantly predict prognosis. A closer investigation into those with extremely impaired cognitive styles found that these were associated with the most chronic and severe forms of eating disorders. Interestingly within the eating disorders group there were subgroups with extreme impairments in one, two or all 3 cognitive styles. Harrison (2010) has provided a visual depiction of these groups, which occur irrespective of diagnosis (See diagram 1.1). As shown, 11% have extreme impairments on all 3 cognitive styles. This group was found to have a significantly longer duration of illness, a lower BMI, a higher EDE-Q score (Eating Disorder Examination Questionnaire; Fairburn and Beglin, 1994) and more obsessive compulsive symptoms (measured by the obsessive compulsive inventory, Foa et al 2002) in comparison to the remaining ED group who either had extreme impairments in one or two cognitive styles.

Diagram 1.1: Venn Diagram Depicting the Proportion of ED Participants who Scored in the Extreme Range for the Cognitive Styles and Social Emotional Profile (Harrison 2010)



1.6.5. Autism model of eating disorders

In line with Harrison's model (2010), which identified subgroups with specific deficits, there is additional evidence to suggest that a subgroup of people with more persistent and severe anorexia nervosa have comorbid autistic spectrum disorder or obsessive compulsive disorder.

A longitudinal study has indicated that within AN, 37% have ASD or cluster C personality disorders which involve severe problems with social interaction compared with only 10% in the control group (Gillberg, Rastam and Gillberg 1996). Furthermore, these people with anorexia nervosa and ASD features are associated with poorer psychosocial functioning (measured by the Modified Morgan Russell scales; Ratnasuriya et al 1991 and the General Assessment of Functioning scale according to DSM-IV criteria) and a longer duration of illness (Wentz 2001; Wentz 2005). These problems in social interaction and obsessive compulsive behaviour are relatively stable traits of the AN phenotype since they were found to be present even after a 10 year follow up (Wentz 2005; Gillberg, Rastam and Gillberg 1996). This subgroup displays a neuropsychological profile reminiscent to that found in autism and aspergers syndrome (Gillberg, Gillberg, Rastam and Joahannsen 1996).

A critique of this model is worth highlighting. The cohort of women investigated by Gillberg and colleagues were assessed for ASD post AN onset. As of yet there is no evidence to indicate that these conditions exist premorbidly or increase the risk of developing AN. Notably research into child and adolescent samples with AN have failed to find a neuropsychological profile

reminiscent of autism. Instead, these samples had superior executive functioning (Hatch et al 2010). In addition adolescent females with eating disorders (sample aged 8-16 of which 91% had AN) did not have a higher prevalence of ASD (Pooni et al 2012). However, there is evidence of some autistic features such as resistance to change and compulsive behaviours being present, although no difficulties in communication (Pooni et al 2012). It is possible that autistic features arise or are exaggerated after the ED onset. This would confer with previous research which has shown features characteristics of autism, such as weak central coherence (Roberts, Tchanturia and Treasure, 2011) and emotional processing abnormalities (Harrison et al 2009) to be exaggerated in the illness state. Therefore it is unclear whether these features are merely a consequence of the acute state or represent a premorbid or comorbid psychiatric diagnosis in itself. However in the absence of longitudinal studies this question remains to be answered.

1.7. Genetic basis of eating disorders

The focus of the present thesis is to explore whether genetic factors contribute to the previously outlined aetiological models by investigating specific risk phenotypes in a genetically informative sample. Research has demonstrated the genetic component to eating disorders. The heritability of narrowly defined AN as specified by DSM-IV criteria varies between 22% to 62% (Mazzeo et al., 2009, Bulik et al., 2006; Bulik et al 2010). The heritability for narrowly defined BN and binge eating disorder has been found to be 62% and 56% respectively (Bulik et al 2010; Javaras et al 2008). Although these studies indicate a strong genetic component, it should be noted that the heritability estimates across studies vary substantially. This may be due to the substantial heterogeneity within the over arching diagnostic categories of AN and BN. Heritability estimates for AN are more likely to be stable cross culturally in comparison to BN, suggesting a stronger genetic component (Keel and Klump 2003). The socio-cultural changes surrounding weight concern and surge in palatable foods may account for the increase in bulimia nervosa over the 19th century (Habermas, 1989).

1.8. Diagnostic difficulties

Due to the complex aetiology of eating disorders, it is not unexpected that this transfers to its classification and diagnosis. At this time eating disorders are diagnosed on the basis of their visible phenotypes. These include core eating disorder problems experienced such as being underweight in AN or binge eating in BED and over or under control of eating in AN and BN respectively. The assignment to diagnostic categories serves to communicate clinical information, to choose the most effective intervention and to predict prognosis (First et al 2004). However diagnosis and subsequent treatment on the basis of visible symptoms may not be a useful device due to the wide heterogeneity within each diagnostic category and frequent fluctuation in symptoms over time (Treasure, Claudino and Zucker, 2010; Eddy et al 2008; Mazzeo et al 2009). As many as 55% of patients who initially suffer with restricting AN (i.e. AN-R) subsequently develop the binge-purge subtype of AN (i.e. AN-BP), BN or EDNOS (Eddy et al

2008). Personality factors such as low self directedness and environmental factors such as high parental criticism are associated with diagnostic crossover from AN to BN (Tozzi et al 2005)

Many patients do not satisfy all of the diagnostic criteria to attain a clinical diagnosis as specified by the DSM-IV or ICD-10 criteria. Amenorrhea is an unreliable diagnostic marker since menstruation may occur below the underweight threshold and regularity can be influenced by medication such as the contraceptive pill. In addition a subgroup of those with AN do not experience an intense fear of weight gain or a distorted body image (Strober et al. 1999). Furthermore the frequency of binge eating may not be attained for it to be diagnosed. A proposal for the DSM-V is that the frequency of binge eating be reduced to one episode per week.

In addition to the aforementioned overt clinical symptoms that occur in EDs there are the secondary areas of disability which are overlooked by current diagnostic criteria. For example poor psychosocial functioning is a common feature (Wentz et al 2009) as is social isolation (Takahashi et al 2006). In the acute state there are elevated levels of obsessive compulsive behaviours (Crane et al 2007), increased anxiety (Godart et al 2000; Kaye et al 2004) and sensitivity to punishment (Harrison et al 2010a). The prevalence of impulsive behaviours is also elevated, and varies across the eating disorder spectrum with the highest incidence in those marked by binge eating and the lowest in restrictive types (Harrison et al 2010d; Fernandez-Aranda et al 2009; Matsunaga et al 1998; Boisseau et al 2009; Claes et al 2001). Most importantly, potential endophenotypes such as cognitive and emotional styles where people with eating disorders deviate from the norm (explained in detail in sections 1.16 to 1.19) are not included in the current DSM or systematically used in the diagnostic process.

A further complication in understanding eating disorders is the impact that the symptoms themselves have on the brain, body and social networks of the individual, either directly or indirectly through psychogenic mechanisms. The brain itself has high caloric needs and undergoes profound changes in response to malnutrition, a problem that is particularly relevant to anorexia nervosa. Depression and anxiety are amplified by the physical impact of extreme weight loss. Also the disruption of eating behaviour (fasting, purging) is known to produce more widespread changes in behaviour and brain biology in animal models (Rada et al 2005; Avena et al 2005; Boggiano et al 2007; Boggiano et al 2005; Avena & Hoebel 2003; Corwin 2006; Corwin & Hajnal 2005). Furthermore disturbed eating behaviours produce profound interpersonal effects, by impacting on close others and prompting reactions towards the symptoms (Treasure et al 2008). These secondary consequences serve to maintain the illness and may be important components of the diagnostic process.

1.9. Classification of eating disorders

To address diagnostic difficulties there have been various proposals for the re-classification and categorisation of eating disorders. The current diagnostic system for AN and BN is on the basis of overt symptoms and this has not changed substantially since 1987 (Walsh and Sysko 2009). A review of the current classification system is underway since the new DSM- V is to be delivered in 2013.

There have been numerous proposals for the DSM-V. For AN it is proposed that the DSM-IV criteria of weight loss leading to the maintenance of body weight less than 85% be changed to a more flexible criteria of a significantly low body weight. Furthermore amenorrhoea will no longer be required to attain this diagnosis. For BN the criteria for binge eating and inappropriate compensatory behaviours both to occur, on average, at least twice a week for 3 months has been reduced to once a week. In addition the distinction between purging and non-purging AN or BN types may be discarded. Binge eating disorder will now acquire its own distinct category and there will be an additional category; avoidant/restrictive food intake disorder characterised by an apparent lack of interest in eating or food and an excessive concern about the aversive consequences of eating.

1.9.1. Classification of eating disorders on the basis of behaviours

The transdiagnostic perspective proposed by Fairburn and colleagues (2003) outlines a broader conceptualisation of EDs. The major clinical features of rigid eating rules and over evaluation of weight and shape are present in all ED's. (Fairburn, Cooper and Shafran, 2003). Moreover there is considerable overlap in their maintaining factors which include perfectionism, low self esteem, mood intolerance and interpersonal factors.

However, others argue against transdiagnostic models as there is strong evidence to warrant the separation of some EDs (Williamson, Gleaves and Stewart, 2005). Research using taxonometric analysis has indicated that anorexia restricting types are qualitatively different from other ED's since it is on a continuum with normality. On the other hand ANBP is more similar to and on a continuum with BN (Gleaves, et al. 2000). This is due to the binge eating component which makes these disorders qualitatively different from normalcy and anorexia restricting types (Williamson, Gleaves and Stewart, 2005).

A middle ground between transdiagnostic and uni-dimensional approaches is the 'broad categories for eating disorder diagnosis' system (BCD-ED) proposed by Walsh and Sysko (2009). This system is argued to reduce the need for the EDNOS category whilst preserving a three category system that resembles the DSM-IV: 1) AN and behaviourally similar, 2) BN and behaviourally similar and 3) binge eating disorder and behaviourally similar (Walsh and Sysko 2009).

1.9.2. Classification of eating disorders on the basis of personality traits

Categorising EDs on the basis of their associated personality traits has also been investigated. A review has shown that both AN and BN are consistently characterised by perfectionism and obsessive compulsiveness. The defining features of AN are high constraint persistence and low novelty seeking whereas BN is associated with higher impulsivity, sensation seeking and novelty seeking (Cassin and Ronson, 2005). There is also a behavioural distinction to be made within AN, with binge purge types having a higher prevalence of impulsive behaviours (such as substance abuse) than restrictive individuals (Krug et al 2009).

Other research (Clifton and Norring, 2005) clustered EDs into 3 categories based on behavioural features. This included anorexics, overeaters and generalised eating disorder. These categories generated larger differences (or higher effect sizes) between groups for perfectionism and disturbed impulse regulation measured by the EDI-2 [(eating disorder inventory; Garner, 1992), Clinton and Norring, 2005]. This suggests that distinguishing eating disorders on the basis of their behavioural features may refine and capture more accurate categories.

The gold standard method used to classify personality in eating disorders is Latent Profile Analysis (LPA). Three studies have adopted this method in eating disorders. Wonderlich and colleagues (2005) applied this method to BN and sub-threshold patients and found three main clusters; 'affective-perfectionist', 'impulsive' and a 'low comorbid psychopathology' cluster. Another study which applied LPA to AN patients distinguished 3 classes; 1) low symptom, 2) elevated drive for thinness, body dissatisfaction, neuroticism, trait anxiety, and harm avoidance and 3) elevated anxious/perfectionistic traits (Jacobs et al 2009). A study which conducted LPA in eating disorder patients including AN, BN and EDNOS found 6 profiles: 'self-focused', 'inhibited', 'average', 'impulsive', adaptive' and 'maladaptive'. The 'inhibited' and 'maladaptive' profiles were found to have the highest levels of ED symptoms and impulsive behaviours. It was concluded that these profiles may provide a more meaningful categorisation of eating disorders (Krug et al 2011).

With such varied proposals on the agenda, it is clear that further investigations are needed to inform the specific causes of these conditions with a view to informing a more robust classification system.

1.10. The concept of endophenotypes

Due to the aforementioned difficulties in diagnosis on the basis of visible phenotypes (section 1.8), an increasingly popular approach in psychiatry has been to investigate endophenotypes. These include personality or neurocognitive traits. Treasure et al (2007) proposed that premorbid risk phenotypes include dysregulated 1) cognitive styles, 2) emotional processing and 3) reward sensitivity. These endophenotypes may be acquired as a consequence of

environmental effects over development or they may be innate and related to the genes; so called endophenotypes (Gottesman and Gould 2003). Endophenotypes may also involve an interaction between environmental factors and risk genotypes such as low functioning serotonin alleles which increase the risk of anorexia nervosa (Karwautz et al 2011). In this case environmental factors could include prenatal, cultural, social and interpersonal factors (Treasure, Claudino and Zucker, 2010). The consequences of malnutrition, abnormal eating and depressive or anxious symptomatology, post onset can exaggerate some of these anomalies and serve to maintain the symptoms (Schmidt and Treasure 2006).

It can be difficult to disentangle these primary and secondary effects as there has been very little longitudinal research. One solution has been to investigate people who have recovered from the illness, with the assumption that any traits they manifest may represent the underlying biological vulnerability. However this assumption may be flawed for several reasons; for example the group who have recovered may have had a different form of illness to those that remain chronically ill, they may continue to have scars from the illness or alternatively treatment may have remediated some areas of difficulty. In the absence of informative prospective studies it is interesting to examine genetically informative samples such as first degrees relatives and twins. It is possible using these multiple methods of study to parse out which traits are premorbid genetic risks and those that are the consequence of or exacerbated by the illness state.

Although the endophenotype and biomarker concepts have been used interchangeably in the literature, Gottesman and Gould (2003) use the former when there are some signs of heritability and use biomarkers when the trait does not fulfil the criteria of genetic underpinnings. Endophenotypes exist between the genes, which are expressed at the biological level and the phenotypes which are expressed at the behavioural or physiological level (See diagram 1.2). It is hoped that endophenotypes will provide a more direct association with the genotype than the phenotypes of eating disorders.

Diagram 1.2: Pathway Between the Genotype and Phenotype

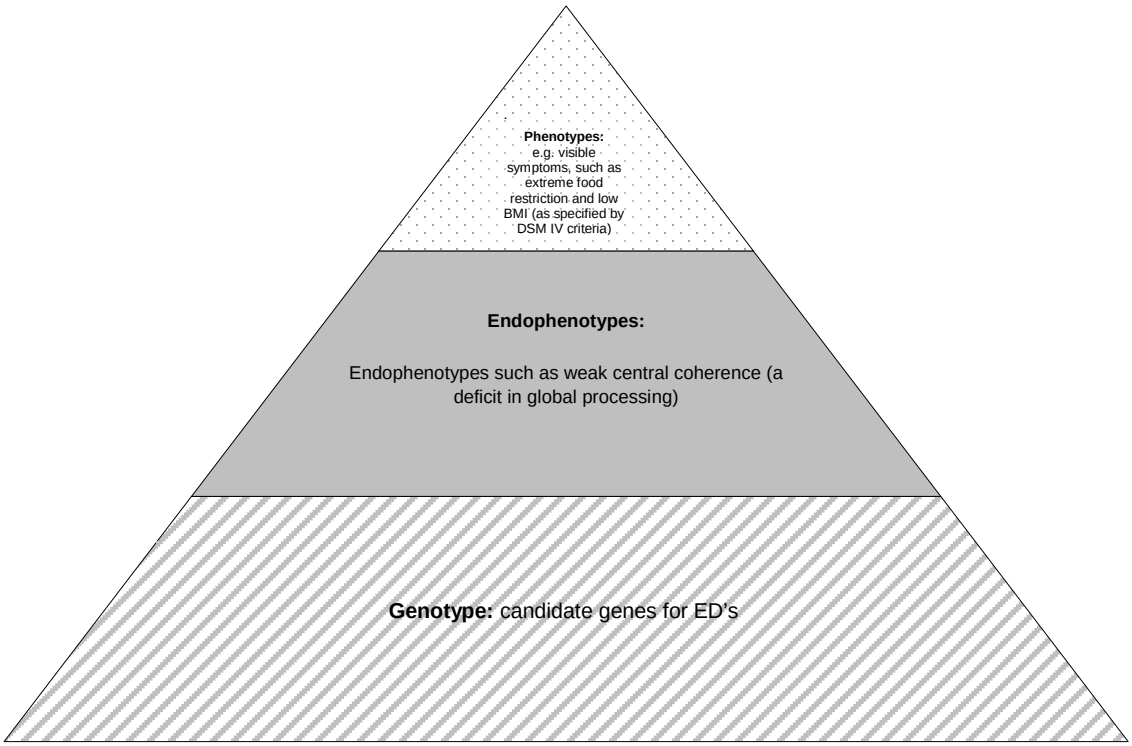


Diagram 1.2: shows how endophenotypes lie on the pathway between candidate genes (genotypes) that increase susceptibility to eating disorders' and visible symptoms (phenotypes). Potential endophenotypes such as "weak central coherence" (which refers to deficits in global processing) maybe more directly associated with eating disorder aetiology. Weak central coherence may be involved in causing and maintaining visible symptoms such as the inability to see the adverse consequences of extreme food restriction on physical health.

Several criteria should be met to attain endophenotype status (see table 1.3). Firstly, the endophenotype should be associated with the illness in the population. Secondly, the endophenotype should be heritable. Thirdly, the endophenotype should be manifested in the individual whether or not the illness is active. Fourthly, within families the endophenotypes and illness should co-segregate. Lastly, the endophenotype will be found in affected and non-affected family members at a higher rate than in the general population (Gottesman and Gould 2003).

Table 1.3: Endophenotype Criteria (Gottesman and Gould 2003)

Endophenotype criteria
1. • Association with the illness in the population
2. • Heritability
3. • State-independence
4. • Co-segregation with the illness in families
5. • Presence in unaffected relatives at a higher level than in the general population

The above criteria must be satisfied for the trait to be classified as an endophenotype.

1.11: Endophenotypes: familial and twin studies

Various methodologies have been adopted to investigate endophenotype criteria in potential risk traits. The first criteria (as specified in table 1.3) has been investigated by comparing clinical samples with controls on risk traits. The third criteria have often been investigated by assessing whether the trait persists in the individual, post recovery. The fourth, fifth and to some extent the second endophenotype criteria can be investigated with familial studies. These refer to those which compare probands and their 1st degree relatives' (i.e. unaffected siblings) to a control population. It is expected that unaffected siblings of the probands will be behaviourally similar since they share 50% of genes as well as environmental influences such as parenting styles and culture. However these studies do not necessarily parse out the effects of shared genes from shared environment thus leaving the second criteria of heritability only partially addressed.

Twin studies allow us to test the second endophenotype criteria of heritability. It was Francis Galton who first proposed twin studies as a method of determining the effects of nature and nurture in 1875. This instigated the 'nature versus nurture' debate. Twin methodology is based on three central assumptions. The first is that the effects of additive genetics are greater for monozygotic twins in comparison to dizygotic twins. Since monozygotic twins have developed from a single egg and share 100% of genes any differences between them are assumed to be due to environmental factors. Nevertheless, it is noted that the assumption of monozygotic twins being genetically identical may not always be accurate since biological factors such as epigenetics can contribute to genetic differences within monozygotic twins (Bruder et al. 2008; Singh, Murphy and O' Reilly, 2002). On the other hand, differences between dizygotic twins who have developed from two fertilized eggs and share 50% of genes (similar to normal siblings) are assumed to be due to both genetic and environmental factors. The second assumption is that of 'equal environments', which proposes that monozygotic and dizygotic twins are equally correlated for their exposure to environmental influences. The equal environments assumption is not without criticism since various incidents can violate this, pre and post-natally (Plomin, DeFries, McClearn & McGuffin 2001). To illustrate a study of the intrauterine environment found that monozygotic twins concordant for schizophrenia were more likely to have been monochorionic (shared the same placenta) as opposed to those who were dichorionic pairs

(Reed et al 1991). However twin studies of eating disorders suggest that the equal environments assumption is not violated (Bulik et al 2000). The third assumption is that the trait is not subject to assortative mating (Neale et al. 1998). A comparison of within pair similarity between monozygotic and dizygotic twins provides a heritability estimate; i.e. the proportion of phenotypic variance that is attributable to genetic factors.

Larger twin studies such as that conducted in chapter 2 can estimate the phenotypic variance attributable to 1) Genes (A: additive genetics) which refers to the effect of several genes influencing the liability of a trait, 2) Shared environment (C: common environment) which refers to factors such as education or parenting styles which both twins are exposed to and contribute to their similarities 3) Unique environmental factors (E: unique environmental effects) which refers to factors that only one twin is exposed to. The accuracy of heritability estimates in humans is not without criticism. In comparison to human studies, those of animals or plant breeding such as those conducted by Gregor Mendel in 1866 can accurately estimate the phenotypic variance, since the differential environments (i.e. conditions) are controlled for. Although Mendel's' experiments on plants were initially ignored, their rediscovery signified the beginning of genetic science. In more recent studies of humans, we are not able to assign genotypes (individuals) to specific environments (Kempthorne 1997). In human studies, only observation can occur. Therefore the accuracy of heritability estimates is subject to gene-environment interaction and unique environmental factors.

The contribution of genes varies widely across traits, disorders and even age. Research has indicated significant increases in genetic influences with advancing pubertal development (Klump et al 2007). During ages 30 to 50, personality stabilises and the contribution of genes increases (Rebollo and Boomsma 2006). This developmental factor is especially relevant since the onset of eating disorders is most prevalent during adolescence.

'Single gene disorders' such as Phenylketonuria (PKU) (which is an autosomal recessive inborn error of phenylalanine metabolism resulting from deficiency of phenylalanine hydroxylase) have relatively simple patterns of heritability caused by mutations in the *PAH* gene (Williams, Mamotte and Burnett, 2009). Others have more complex patterns of heritability such as that seen in psychiatric disorders where a variety of genes contribute to susceptibility and only specific traits are heritable (Marshall et al 2008).

Some have argued that twin populations are not comparable to singletons due to the differential prenatal and postnatal environments. Obstetric complications in twin samples have been associated with an increased risk of BN and AN. Furthermore gestational age was associated with an increased risk of AN (Foley et al 2001). Secondly, differential sibling interaction may be especially the case for monozygotic twins as a result of their identical physical appearance. However research, which has investigated whether the heritability of certain traits may be

attributed to this competitiveness, has found it to be a negligible factor (Rebollo and Boomsma 2006). Furthermore studies of the heritability of physical attributes and diseases have concluded that the results of twin studies can be generalised to singleton populations (Andrew et al 2001).

There are also the practical difficulties of obtaining monozygotic and dizygotic twins. It has been highlighted that the number of dizygotic twins in the Caucasian population have been declining over the past 50 years and this cannot be explained by ascertainment bias (Hur, McGue and Lacano, 1995).

Adoption studies provide the most powerful family design since any similarities between the child and adoptive parent can be directly attributed to environmental factors. Furthermore genetic factors can be determined by similarities between the child and biological parents (Plomin et al 2001). One study employing this method found increased risk of schizophrenia in adopted children who had biological relatives with schizophrenia (Kendler and Gruenberg 1984). However obtaining such a unique sample can prove difficult and is beyond the scope of the present thesis.

Molecular genetic investigations are also beyond the scope of the present thesis. In comparison to twin studies, which demonstrate the heritability of traits, linkage and association studies utilise information about heritability to help search for specific genes that are associated with these traits.

1.12. Endophenotypes in eating disorders

The aim of the following sections is to present the current evidence of potential endophenotypes in people with eating disorders. Findings in the acute state and wherever possible in the recovered state are also reported to remove some of the confounding changes that occur in the acute state due to malnutrition or other eating disorder symptoms. As yet there is no evidence measuring these traits before onset. Also reviewed are studies which have examined these traits in 1st degree relatives. Finally, given the negligible research linking these neurocognitive traits with a biological foundation, a synthesis of research exploring the biological and genetic basis of these traits in eating disorder samples is presented. Evidence of these traits in conditions that are comorbid with eating disorders is also provided. These include attention deficit hyperactivity disorder (ADHD) (Seitz et al 2011), autistic spectrum disorder (ASD) (Wentz et al 2005), obsessive compulsive disorder (OCD) (Godart et al 2006), depression (Godart et al 2007), anxiety disorders (Kaye et al 2004) and addictions (Krug et al 2009).

1.13. Personality and behavioural profiles

Perfectionistic and obsessive compulsive traits consistently characterise both AN and BN (Anderluh et al 2009). The defining features of AN are high constraint persistence and low novelty seeking whereas BN is associated with higher impulsivity, sensation seeking and

novelty seeking (Cassin and Ronson, 2005). These defining features will be explored in terms of their endophenotypes status in the following sections.

1.14. Definition of obsessive compulsive personality features

Research into psychiatric disorders and control samples has investigated the presence and genetic basis of obsessive compulsive personality disorder (OCPD) or obsessive compulsive disorder (OCD). Research has also investigated features that reflect these conditions, such as 'traits reflecting an obsessive compulsive personality' (OCP) or 'obsessive compulsive traits' as opposed to the presence of the entire diagnosis itself.

The DSM-IV-TR has defined OCPD as a preoccupation with orderliness, perfectionism and mental and interpersonal control at the expense of flexibility, openness and efficiency, beginning in early childhood (DSM-IV TR; American Psychiatric Association, 2000).

OCD has been defined as an anxiety disorder that exhibits obsessive or compulsive behaviours. In this context obsessions are defined as persistent thoughts, impulses, or images that are experienced as intrusive and cause marked anxiety. The thoughts are not simply excessive worrying. The person may try to neutralise the thoughts with another thought or action. Compulsions are defined as repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession. The compulsion will reduce or prevent the individual's anxiety, even though the compulsion and its resultant anxiety reduction may not be logically linked.

1.14.1. Obsessive compulsive personality features in relation to eating disorders symptoms

Features reflecting OCP and OCD are known to inform the risk and progression of eating disorders. Within eating disorders, OCP traits may manifest in high levels of perfectionism and chronic doubt. Furthermore the behavioural inflexibility aspects of OCP may manifest in ritualised and repetitive behaviours such as exercising compulsively, calorie counting, body checking and food rituals (Sherman et al 2006; Steinglass and Walsh 2006; Drewnowski, Pierce and Halmi, 1988).

1.14.2. Neural correlates of obsessive compulsive personality features

Underlying repetitive behaviours and compulsive symptoms seen in both OCD and anorexia nervosa are possible deficits in implicit learning (an executive function of the frontal lobe). This refers to difficulties in learning new behaviours, which are mediated by the cortico-striatal circuits (Steinglass and Walsh 2006).

Research has found compulsive symptoms such as checking, washing and hoarding to be associated with distinct parts of the frontostriatothalamic circuits which have been previously implicated in cognitive and emotional processing (Matiax-Cols et al 2004).

1.14.3. Obsessive compulsive personality features in eating disorders

The EATATE lifetime diagnostic interview (Anderluh et al 2003) was developed to systematically assess childhood behaviours reflecting an OCP in eating disorders (i.e. OCP features). Research using this instrument has found elevated levels of OCP traits in eating disorders, with the highest prevalence in AN-R (Anderluh et al 2003) and anorexia nervosa purging type (AN-P) (Halmi et al 2011). A different self report instrument (Childhood risk factors questionnaire: Kim, Heo, Kang, Song and Treasure et al. 2010) found retrospective accounts of elevated pre-morbid anxiety and perfectionism to be equally prevalent in a Korean sample with AN (Kim, Heo, Kang, Song and Treasure et al. 2010). OCP traits (measured by the EATATE) have also been found to be associated with specific behavioural traits such as body dissatisfaction and drive for thinness (eating disorder inventory version 2, Garner, 1992) as well as ICD-10 (WHO, 1992) defined symptoms of anorexia nervosa (Halmi et al 2011).

OCP features appear to occur pre-morbidly. Studies using the self- report version of the EATATE (childhood retrospective perfectionism questionnaire) have found by regression analysis that pre-morbid obsessive compulsive personality traits are a strong predictor of developing an eating disorder (Southgate et al. 2008). The risk of developing an eating disorder increased 6.9 times with every additional OCP trait reported using the interview method (Anderluh et al 2003). Inevitably retrospective reports of premorbid traits are biased. For example the individual may search for possible factors that contributed to the development of an eating disorder. However others have also found OCPD (DSM-II-R diagnoses) to exist prior to onset in 35% of those with AN (Rastam 1992).

OCP features are also positively associated with the severity of behavioural and psychopathological eating disorder symptoms. Behavioural inflexibility in childhood and perfectionism was associated with a longer duration of dieting, fasting, duration of AN and a shorter duration of binge eating (Anderluh et al 2009). Similarly rule-bound traits in childhood have been associated with longer periods of being underweight and excessive exercising (Anderluh et al 2009). Furthermore OCP traits have been associated with the eating disorder neurocognitive profile, specifically weak central coherence referring to a detail focused processing style (Lopez, Tchanturia and Treasure 2008d) and poor set shifting which indicates cognitive inflexibility (Tchanturia, et al 2004; Roberts, Tchanturia and Treasure 2010).

A longitudinal investigation (Nilsson, Gillberg, Gillberg and Rastam, 1999; Rastam, Gillberg and Gillberg 1995) has shown that co-morbid obsessive compulsive behaviours characterise the more chronic forms of anorexia nervosa with poorer outcome (measured by the Morgan Russell scale) (Nilsson, Gillberg, Gillberg and Rastam, 1999; Rastam, Gillberg and Gillberg 1995). In this cohort of adolescents with anorexia nervosa, OCD traits combined with empathy disorders, more accurately predicted outcome in terms of recovery, physical symptoms and social relationships than the AN diagnosis itself (Gillberg, Rastam and Gillberg, 1995).

1.14.4. Obsessive compulsive personality features in eating disorders: familial traits

Co-segregation of eating disorders and OCP traits within families has been investigated using genetically informative samples such as first degrees relatives. Evidence indicates that OCP traits are familial risks since perfectionism (Multi dimensional perfectionism scale; Frost, Marten, Lahart and Rosenblate, 1990), OCPD (measured by the SCID; structured clinical interview for psychiatric disorders, Spitzer, Williams, Gibbon and First, 1990) and OCD (measured by the National Institute of Mental Health Diagnostic Interview Schedule) are elevated in unaffected family members (Woodside et al 2004; Lilenfeld et al 1998; Bellodi et al 2004).

Furthermore, poor set shifting- a marker of behavioural flexibility and obsessive compulsive symptoms appears to be a familial trait as it was found in unaffected sisters of those with an eating disorder (Roberts, Tchanturia and Treasure 2010). The familial liability of these traits is the product of shared genes as well as environmental factors.

1.14.5. Obsessive compulsive personality features in eating disorders: biological underpinnings

Twin studies assessing the specific contribution of genes have found perfectionism to be heritable (Wade et al, 2008). Molecular genetic studies have gone on to implicate the 5-HT2A receptor gene in increasing the shared risk of both AN and OCD behaviours such as harm avoidance, perfectionism and obsessionality (Enoch et 1998; Rybakowski et al 2006). Furthermore, genetic studies have found that the dopamine receptor gene which is associated with dysfunctional eating in AN, is also associated with personality traits such as perfectionism (Bachner-Melman et al 2007). This suggests that risk genotypes associated with serotonin and dopamine functioning may predispose an individual to OCP traits and the risk of developing anorexia nervosa. Although it is noted that specific genes often account for relatively little variance in psychiatric traits (Gottesman and Gould, 2003).

The aetiology of the aforementioned traits in eating disorders is often accounted for by an interaction between an initial genetic predisposition and environmental factors. For example early life precipitants including perinatal factors such as the maternal reporting of stress during pregnancy has been associated with cognitive inflexibility and perfectionism in AN (Favaro and Santonastaso, 2010; Favaro and Santonastaso, 2008). Other research has also confirmed the association between perinatal and postnatal factors and the expression of OCD (Vasconcelos et al. 2007).

1.15. Impulsive behaviours

1.15.1. Definition of impulsive behaviour

Impulsivity is an umbrella term encompassing urgency, sensation seeking, lack of premeditation and perseverance (Whiteside and Lynam 2001). These maladaptive behaviours often involve an altered sensitivity to reward whereby there is ‘wanting’ without necessarily wanting to do so

at the more cognitive and conscious level. Addictive behaviours provide a suitable illustration of this concept. In this case 'wanting' occurs by way of an incentive that involves sensitization of the mesolimbic dopamine system and connected structures (Berridge, 2007).

1.15.2. Impulsive behaviour in relation to eating disorder symptoms

Impulsive behaviours have been found in all eating disorders, although are most prevalent in those marked by binge eating in comparison to restrictive types (Favaro et al 2005; Fernandez-Aranda et al 2008). Patients with BN tend to show higher levels of impulsivity than patients with AN (Boisseau et al 2009; Claes et al 2001). However comparisons between AN subdiagnosis have shown differences on measures of impulsivity, with ANBP types generally exhibiting higher levels of impulsivity than individuals with AN-R (Eddy et al 2002).

Impulsive behaviours include purging; specifically vomiting and this has been associated with personality traits of novelty seeking and lower levels of perfectionism (Reba et al 2005). Outside of dysfunctional eating patterns impulsive behaviours may also manifest as self-injury, substance abuse and suicide (Favaro et al 2007; Dunn et al 2002; Fernandez-Aranda et al 2006).

Patients with bulimia nervosa tend to show higher levels of impulsivity in comparison to patients with anorexia nervosa (Boisseau et al 2009; Claes et al 2001). However a comparison between ANR and ANBP has shown no overall differences on measures of impulsivity which included alcohol abuse, drug abuse and suicideality. It is noteworthy that within this study 62% of those with ANR had crossed over to ANBP at an eight year follow up (Eddy et al 2001). Research has led to the suggestion that there may exist a subgroup within bulimia nervosa who is genetically predisposed to much higher levels of impulsivity (Fernandez-Aranda et al 2008; Matsunaga et al 1998). In support, research has found that 23% of those with BN have a comorbid diagnosis of impulse control disorder (Fernandez-Aranda et al 2006).

Whilst impulsivity distinguishes between diagnostic groups, it may also be predictive of the longitudinal course of the illness. Impulsivity, in addition to symptom severity, and chronicity was found to explain 45% of the variance in unfavourable outcomes at a 12 year follow up of women with anorexia nervosa (Fichter, Quadflieg and Hedlund, 2006). Research indicates that people with bulimia nervosa and comorbid multi-impulsive behaviours or impulse control disorder (ICD) have a slower response to treatment, more severe eating disturbances and pathological personality disturbances (Fahy and Eisler, 1993, Fernandez-Aranda et al 2008, Fernandez-Aranda et al 2006). Impulse control disorders are also predictive of still having bulimia nervosa at a 10-year follow up and length of time since their most recent binge/purge episode (Keel et al 2000).

1.15.3. Impulsive behaviours in eating disorders: familial traits

Studies of genetically informative samples such as twins and sibling pairs indicates that traits related to impulsive behaviours such as sensitivity to reward (Wade et al 2008; Karwautz et al 2002) and novelty seeking are familial risks (Wade et al 2004). Studies have also shown higher rates of alcohol and substance use disorders in family members of women with bulimia nervosa (Bulik, 1991; Kaye et al 1996)

1.15.4 Impulsive behaviours in eating disorders: biological underpinnings

The extent to which reward sensitivity and impulsivity is the consequence of environmental factors or genes has been investigated. In representative samples a review has found a consensus of 45% of the variance in impulsivity, assessed by self-report measures, to be accounted for by genetic factors (Congdon and Canli, 2008; Hur and Bouchard, 1997; Pedersen, Plomin, McClearn & Friberg, 1998).

Molecular genetic studies of bulimia nervosa have found evidence that gene environment interaction may contribute to impulsivity. Women with bulimia nervosa who are carriers of the 5HTTLPR s-allele and report a history of sexual or physical abuse show elevated levels of affective instability and impulsivity (Steiger et al 2008). Previously, research has linked impulsivity in bulimia nervosa with reduced 5-HT reuptake (Steiger et al 2003).

Furthermore, other research found the co-morbidity between bulimia nervosa and drug use to be mostly accounted for by heritable factors (genetic factors: 83%, non-shared environmental factors: 17%) (Baker et al 2007).

Studies of representative samples indicate that disinhibited eating behaviour such as bingeing and purging has been associated with an increased frequency of the G allele of the 5HT2A receptor gene -1438A/G polymorphism (Nishiguchi et al 2001). Women who carry the BDNF Met-allele are more prone to binge eating in response to severe food restriction (Akkermann, Hiio, Villa and Harro 2010).

1.16. Cognitive styles

Overall people with AN have above average cognitive abilities predominantly in regard to verbal abilities (measured by the NART; Nelson and Wilson, Lopez et al 2010; Tchanturia et al 2005; Southgate, Tchanturia and Treasure, 2006). Other abilities used to generate an IQ score for the Weschler scales, such as mixed verbal and visual spatial abilities are reported to be impaired in AN (Southgate, Tchanturia and Treasure, 2006). In line with these latter impairments, research has demonstrated specific cognitive features to exist in eating disorders, which includes poor set shifting and weak central coherence.

1.17. Set shifting

1.17. 1. Definition of set shifting

Cognitive flexibility, when applied to real life encounters has two aspects which are spontaneous and reactive flexibility. Spontaneous flexibility refers to the ability to generate diverse and creative responses and bypass habitual strategies in response to a single task. Reactive flexibility refers to the ability to readily shift cognitions and behaviour according to the changing demands of a situation (Eslinger and Grattan 1993).

1.17.2. Neural correlates of set shifting

Miller and Cohen (2001) argue that set shifting functions are dependent on the prefrontal cortices' (PFC) ability to co-ordinate activity in other parts of the brain. Studies using FMRI (functional magnetic resonance imaging) in control samples have shown that the dorso-lateral prefrontal cortex (DLPFC) is actively engaged when switching between rules (Ravizza and Carter, 2008). Moreover damage to the dorsolateral frontal lobe is associated with an impaired ability to adapt to new rules on the WCST task [Wisconsin Card Sorting Test; Heaton et al., 1993, (Milner, 1963)].

1.17.3. Set shifting in relation to eating disorders symptoms

People with eating disorders have features such as rule bound behaviour (excessive compliance with rules set by parents and teachers) and behavioural inflexibility (difficulties in adjusting to change or making contingency plans) that exist premorbidly (Anderluh et al 2003) and in adolescence (McNarney et al 2011). These features are suggestive of problems in cognitive flexibility. The degree of chronicity, severity and response to treatment in anorexia nervosa has been associated with features linked to cognitive and behavioural inflexibility (Anderluh et al 2009).

In the acute state, cognitive inflexibility can manifest itself through ritualised and repetitive behaviours. Inflexible rule-driven eating patterns may involve counting calories and using numbers to manage eating behaviours as well as avoiding certain foods such as carbohydrates or those high in fat content. Excessive exercising may also occur in a repetitive rule-bound manner (Steinglass and Walsh 2006; Drewnowski, Pierce and Halmi, 1988). In other cases more typical OCD behaviours such as excessive cleaning, ordering and hoarding may occur.

1.17.4. Set shifting in eating disorders: acute state

In an experimental setting, the field of eating disorders has employed a variety of neuropsychological tasks to explore the nature of cognitive flexibility. The WCST (Wisconsin Card Sorting Test, Heaton et al., 1993) and Brixton task (Burgess & Shallice, 1997) have been commonly used (see table 1.4). A systematic review by Roberts et al (2007) concluded that people with eating disorders had difficulties in set shifting.

Following the systematic review by Roberts et al (2007) there have been further studies confirming this association in adults as well as adolescents (Tchanturia et al 2011a; Abbate-Daga et al 2011; Konstantakopoulos et al 2011; McAnarney et 2010; Roberts et al 2010, Teconi et al 2010; Nakazato et al 2010; Nakazato et al 2008). A synthesis of these studies (see table 1.4) indicates that people with eating disorders differ from healthy controls with an overall medium effect size on the WCST (weighted effect size: d= 0.56) and the Brixton task (weighted effect size: d= 0.57).

There are no overall differences between AN and BN for difficulties in set shifting as measured by the WCST (perseverative errors) (weighted effect size AN: d= 0.55; weighted effect size BN: d= 0.54). However, a greater overall deficit on the Brixton task was found for AN (weighted effect size AN: d= 0.45; weighted effect size BN: d= 0.23) (see table 1.4). Differences in set shifting difficulties measured by the Brixton task and the WCST may be explained by the tasks differences in level of complexity. In the WCST task, participants are not given explicit instructions that they will need to adapt to new rules throughout the task, although this is the case in the Brixton task. Furthermore in the WCST, participants are told whether their response is correct, allowing them to learn from feedback (Tchanturia et al 2012). Variations between findings for the WCST and Brixton task across studies is also in part attributed to the use of different versions (pen and paper or computerised) and different outcome variables (number of correct responses, categories completed or number of perseverative errors). Therefore a compilation of all studies from one centre administering these measures in the same manner is of interest. Recent work which sought to do this, found set shifting difficulties in people with eating disorders and found no overall differences between AN and BN in comparison to controls for the WCST (perseverative errors) (AN: d=0.8, BN: d= 0.9) (Tchanturia et al 2012) and a greater overall deficit on the Brixton task in AN (AN: d=0.6, BN: d= 0.3) (Tchanturia et al 2011).

Poor cognitive flexibility measured by the Brixton task and WCST was found to be associated with a longer duration of illness and more severe eating disorder rituals (Roberts et al 2010). Furthermore AN inpatients have greater difficulties on the Brixton task than outpatients (Tchanturia et al 2011). Therefore this phenotype is a marker of prognostic relevance for people with eating disorders.

1.17.5. Set shifting in eating disorders: recovered

Set shifting deficits have been found to persist in recovery although in an attenuated form (Tenconi et al 2010; Nakazato et al 2008; Nakazato et al 2008; Tchanturia, Morris, Anderluh, Collier, Nikolaou, Treasure,2004; Tchanturia et al 2011) (See table 1.4). A synthesis of these studies indicates that people recovered from AN, differ from healthy controls with an overall small effect size on the WCST (perseverative errors) (weighted effect size: d= 0.35) and the Brixton task (weighted effect size: d= 0.33) (see table 1.4). It may be that this deficit is a scar

from the illness. Alternatively it may suggest that it has an innate cause, which is exacerbated as a secondary consequence of poor nutritional status.

1.17.6. Set shifting in eating disorders: familial traits

More recently, studies have assessed the presence of such traits in first degree relatives and have found that they are shared traits (Roberts et al 2010; Tenconi et al 2010) (See table 1.4). A synthesis of these studies indicates that 1st degree relatives of people with eating disorders differ from healthy controls with an overall medium effect size on the WCST (perseverative errors) (weighted effect size: d= 0.49) but only a negligible effect size on the Brixton task (weighted effect size: d= 0.01) (see table 1.4).

1.17.7. Set shifting in eating disorders: biological underpinnings

Biological markers thought to be linked with set shifting abnormalities have been examined in both the acute and recovered state. The biological marker; brain derived neurotrophic factor (BDNF) is known to modulate levels of serotonin and the plasticity of brain mechanisms involved in learning and memory. In AN and BN, levels of BDNF have been found to be attenuated. However there is no association between BDNF serum levels and performance on the WCST in eating disorders (Nakazato et al 2003; Nakazato 2008).

Research investigating the genetic risk of set shifting difficulties in eating disorders has shown that the COMT Val158Met genotype does not moderate set shifting abilities (measured by the Trail Making Task, Reitan, 1955) in eating disorders (Kim, Kim and Kim 2010).

People with anorexia nervosa have abnormal brain activation in the fronto-striato-thalamic pathways during a behavioural response set shifting task. Specifically, there is hypoactivation in parts of the brain involved in motivation related behaviours and over activity in parts of the brain involved in supervisory cognitive control (Zastrow et al 2009).

1.17.8. Set shifting in normal and psychiatric disorders: familial traits

Deficits in set shifting have been found in 1st degree relatives of other psychiatric illnesses such as schizophrenia (Breton et al 2010; Lien et al 2010; Lee et al 2008; Barrantes-Vidal 2007; Szoke et al 2006; Bolte and Poutska 2006; Klemm et al 2006; Thompson et al 2005; Zalla et al 2004; Sitskoorn et al 2004), bipolar disorder (Juselius et al 2009; Trivedi et al 2008; Frantom, Allen and Cross, 2008; Arts et al 2008; Bora, Yucel & Pantelis, 2009), autistic spectrum disorder (Sumiyoshi et al 2010; Bolte and Poutska 2006; Ozonoff et al 1993; Szatmari et al 1993) attention deficit hyperactivity disorder (Bidwell et al 2007; Slaats-Willemse et al 2007; Seidman et al 2000) and obsessive compulsive disorder (Cavedini et al 2010). This suggests that it is a familial risk factor which impacts on a broad range of psychiatric disorders.

1.17.9. Set shifting in normal and psychiatric disorders: biological underpinnings

A meta-analysis of 16 studies (Barnett, Scoriels and Munafo 2008) including control and samples with schizophrenia found a small association between the Val158Met COMT genotype and the WCST perseverative errors in control individuals. Although no overall association was found between the WCST and the COMT 158 Met allele in schizophrenia. This review found that earlier studies of the COMT 158 Met allele in schizophrenia had positive findings of it's' association with the WCST perseverative errors.

In people with ADHD, the WCST perseverative error is associated with a region on chromosome 3q13 and has a modest heritability of 0.18 (Doyle et al 2008).

Table 1.4: Set Shifting in Current and Recovered Eating Disorders and Their 1st Degree Relatives.

	Comparison groups		Test	Findings	Effect size comparison
Current Eating Disorders					
Thompson (1993)	AN (n=10)	Controls (n=10)	WCST PE errors	AN> Controls	(d=0.50)
Fassino et al. (2002b)	AN (n=20)	Controls (n=20)	WCST PE errors	AN> Controls	(d=0.62)
Koba et al. (2002)	AN (n=11)	Controls (n=7)	WCST PE errors	AN> Controls	(d=1.25)
Ohrmann et al. (2004)	AN (n=11)	Controls (n=11)	WCST PE errors	AN> Controls	(d=0.62)
Steinglass, Walsh and Stern (2006)	AN (n=15)	Controls (n=11)	WCST PE errors	AN> Controls	(d=0.04)
Gadas et al (2009)	ED (n=60) Schizophrenia (n=20)	Controls (n=30)	WCST PE errors	ED= Controls ED < Schizophrenia*	
Namyslowska et al (2009) Conference	AN (n=30) BN (n=30)	Controls (n=39)	WCST PE errors	AN> Controls	
Nakazato et al (2010) and Nakazato et al (2008)	AN (N=24)	Controls (n=28)	WCST PE errors	AN > Controls	(d=0.74)**
Roberts et al (2010)	ANR (n=35) ANBP (n=33)	Controls(n=88)	WCST PE errors	ANR >Controls	(d=0.3)
				ANBP > Controls	(d=0.75)**
Tenconi et al (2010)	AN (n=153)	Controls (n=120)	WCST PE errors	AN> Controls	(d=0.41)*
Abbate-Daga et al (2011)	AN (n=30)	Controls (n=30)	WCST PE errors	ANR > Controls ANR = Controls (covaried, BMI, depression and years of education)	(d=0.65)
McAnarney et al (2011)	AN (n=24)	Controls (n=37)	WCST PE errors	ANR < Controls	(d=-0.51)
Tchanturia et al (2011)	AN (n=171) BN (n=82)	Controls (n=171)	WCST PE errors	AN > Controls	(d=0.8)**
			Weighted effect size AN, WCST PE errors: d= 0.55		
Namyslowska et al (2009) Conference	AN (n=30) BN (n=30)	Controls (n=39)	WCST PE errors	BN=Controls	

Roberts et al (2010)	ANR (n=35) ANBP (n=33) BN (n=30)	Controls(n=88)	WCST PE errors	BN > Controls	(d=0.5)*
Bucci et al (2010)	BN (n=83)	Controls (n=77)	WCST PE errors	BN= Controls	(d=0)
Tchanturia et al (2012)	AN (n=171) BN (n=82)	Controls (n=171)	WCST PE errors	BN > Controls	(d=0.9)**
			Weighted effect size BN, WCST PE errors: d= 0.54		
Gadas et al (2009)	ED (n=60) Schizophrenia (n=20)	Controls (n=30)	WCST PE errors	ED= Controls ED < Schizophrenia*	
Harrison (2010)	ED (n=98)	Controls (n=89)	WCST PE errors	ED > Controls	(d=0.72) **
Goddard (2011)	ED Male (n=29) ED Female (n=100)	Control Male (n=42) Control Female (n=90)	WCST PE errors	ED > HC * Males > Females *	
			Weighted effect size EDs (ED + AN + BN), WCST PE errors: d= 0.56		
Holliday et al (2005)	AN (n=47)	Controls (n=47)	Brixton errors	AN < Controls	(d=-0.29)
Roberts et al (2010)	ANR (n=35) ANBP (n=33) BN (n=30)	Controls(n=88)	Brixton errors	ANR >Controls	(d=0.1)
				ANBP > Controls	(d=0.65)**
Konstantakopoulos et al (2011)	AN (n=25), BN (n=15)	Controls (n=35)	Brixton errors	AN > Controls	(d=0.97)*
				AN > BN	(d=0.7)
Tchanturia et al (2011)	AN (n=215), BN (n=69), EDNOS (n=29)	Controls (n=216)	Brixton errors	AN > Controls	(d=0.6)*
			Weighted effect size AN, Brixton errors: d= 0.45 (n=819)		
Tchanturia et al (2004)	BN (n=19)	Controls (n=35)	Brixton errors	BN > Controls	(d=0.07)
Roberts et al (2010)	ANR (n=35) ANBP (n=33) BN (n=30)	Controls(n=88)	Brixton errors	BN =Controls	(d=0.1)*

Konstantakopoulos et al (2011)	AN (n=25), BN (n=15)	Controls (n=35)	Brixton errors	BN > Controls	(d=0.32)*
				AN > BN	(d=0.7)
Tchanturia et al (2011)	AN (n=215), BN (n=69), EDNOS (n=29)	Controls (n=216)	Brixton errors	BN > Controls	(d=0.3)
			Weighted effect size BN, Brixton errors: d= 0.23		
Harrison (2010) Thesis	ED (n=98)	Controls (n=89)	Brixton errors	ED > Controls	(d=0.56) **
Tchanturia et al (2011)	AN (n=215), BN (n=69), EDNOS (n=29)	Controls (n=216)	Brixton errors	EDNOS > Controls	(d=1.7)*
Goddard (2011)	ED Male (n=29) ED Female (n=100)	Control Males (n=42) Control Females (n=90)	Brixton errors	ED > HC *	
			Weighted effect size EDs (ED + AN + BN), Brixton errors: d= 0.57		
Recovered					
Nakazato et al (2010) and Nakazato et al (2008)	Recovered AN (n=18)	Controls (n=28)	WCST PE errors	AN recovered = Controls	(d=0.33)
Roberts et al (2010)	Recovered AN (n=30)	Controls (n=88)	WCST PE errors	AN recovered = Controls	(d=0.15)
Tenconi et al (2010)	AN long term recovered (n=29), AN weight restored (n=63)	Controls (n=120)	WCST PE errors	AN long term recovered > Controls*	(d=0.44)
				AN weight restored > Controls*	(d=0.42)
Harrison (2010) Thesis	Recovered AN (n=35)	Controls (n=89)	WCST PE errors	AN recovered > Controls	(d=0.22)
Tchanturia et al (2012)	Recovered AN (n=90)	Controls (n=199)	WCST PE errors	AN recovered > Controls**	(d=0.4)
			Weighted effect size Recovered AN, WCST PE errors: d= 0.35		
Tchanturia, Morris, Anderluh, Collier, Nikolaou, Treasure (2004)	Recovered AN (n=18)	Controls (n=36)	Brixton errors	AN recovered > Controls	(d=0.34)
Roberts et al (2010)	Recovered AN (n=30)	Controls (n=88)	Brixton errors	AN recovered = Controls	(d=0.05)
Harrison (2010) Thesis	Recovered AN (n=35)	Controls (n=89)	Brixton errors	AN recovered > Controls	(d=0.41)
Tchanturia et al (2011)	Recovered AN (n=72)	Controls (n=216)	Brixton errors	AN recovered > Controls	(d=0.4)

			Weighted effect size recovered AN, Brixton errors: d= 0.33		
1st Degree Relatives					
Roberts et al (2010)	Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	WCST PE errors	Non-AN sisters > Controls	(d=0.58)*
Tenconi et al (2010)	Non-AN sisters (n=28)	Controls (n=120)	WCST PE errors	Non-AN sisters > Controls	(d=0.65)*
			Weighted effect size AN 1st degree relatives, WCST PE errors: d= 0.62		
Roberts et al (2010)	Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	WCST PE errors	Non-BN sisters > Controls	(d=0.18)
			Weighted effect size ED (AN+BN) 1st degree relatives, WCST PE errors: d= 0.49		
Holliday et al (2005)	Non-AN sisters (n=47)	Controls (n=47)	Brixton errors	Non-AN sisters < Controls	(d=-0.46)*
Roberts et al (2010)	Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	Brixton errors	Non-AN sisters = Controls	(d=0.05)
			Weighted effect size AN 1st degree relatives, Brixton errors: d=-0.18		
Roberts et al (2010)	Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	Brixton errors	Non-BN sisters > Controls	(d=0.39)*
,			**Weighted effect size ED (AN+BN) 1st degree relatives, Brixton errors:** d= 0.01		

WCST PE errors (Wisconsin card sorting task Perseverative errors) (Heaton et al., 1993)
Brixton task (Burgess & Shallice, 1997)
** = P<0.001
**= P<0.05

1.18. Central Coherence

1.18. 1 Definition of central coherence

According to the global precedence theory, perception involves a balance between global and local processes. A temporal sequence of perception usually begins with seeing the global structure followed by perceiving the finer details (Navon 1977). The overall balance between global over detail has been termed central coherence and the opposite of this, weak central coherence is considered to be one marker of ASD (Happe and Booth 2008).

1.18. 2. Neural correlates of central coherence

Investigation into the physiological underpinnings of weak coherence in ASD suggests that there may be reduced synchronisation across the cortical network (Frith 2004; Brock et al 2002). Detailed (or local) processing (measured by the Embedded Figures Test; Witkin, Dyk, Faterson, Goodenough and Karp, 1962) in autistic spectrum disorder is associated with greater activation in the ventral occipitotemporal regions (visual systems utilised for object feature analysis) (Ring et al 1999). Parents of those with autism also show superior detail processing and increased activity in the visual cortex (middle occipital and lingual gyri) (Baron-Cohen et al 2006). This contrasts with the comparison group who showed greater activation in the prefrontal cortices (Ring et al 1999).

1.18. 3. Central coherence in relation to eating disorders symptoms

There are several clinical features that are suggestive of enhanced detail processing in people with eating disorders including obsessive-compulsive personality traits and perfectionism (Lopez et al 2008a). Furthermore, difficulties in global integration may contribute to the preoccupation with specific parts of the body and the impaired ability to identify the broader consequences of their disorder such as malnutrition and poor physical health.

1.18. 4. Central coherence in eating disorders: acute state

The vast majority of research into weak central coherence in the field of eating disorders has focused on local processing in the visual domain. Although weak central coherence can also influence performance in other domains such as the processing of music (Mottron, Peretz and Menard, 2000) and linguistics (Joliffe and Baron-Cohen, 1999). In an experimental setting, the field of eating disorders has employed a variety of neuropsychological tasks to explore the two dimensions (strength in detail and weakness in global processing), which contribute to weak central coherence. The most commonly used have been the Group Embedded Figures Task (GEFT, Witkin, Oltman, Raskin, and Karp, 2002), used to assess detailed processing and the Rey Osterrieth Complex Figure Task (ROCF, Osterrieth 1944), used to assess global integration as well as detailed processing (See table 1.5). However, the exact form of administration and scoring procedure used, varies and sometimes is not clearly specified, making the synthesis of the results difficult. Nevertheless, a systematic review by Lopez and

colleagues (2008d) concluded that detailed processing is more dominant than a global strategy in eating disorders. A review of bulimic disorders (BN and BED) concluded that there was some evidence of impairment in these tasks (Van den Eynde et al 2011). Subsequent to the systematic review by Lopez and colleagues (2008d), further studies have confirmed the presence of weak central coherence in women with eating disorders (Roberts et al 2011; Harrison, Tchanturia and Treasure, 2011; Tenconi et al 2010; Lopez et al 2008a; Lopez et al 2008c). A synthesis of these studies indicates that people with eating disorders differ from healthy controls with medium effect sizes on the GEFT(modified version by Happe´ & Booth, 2008) (weighted effect size: d= -0.43) and the ROCF task (Booth 2006 scoring method) (weighted effect size: d = -0.60) (see table 1.5).

A synthesis of studies that have used the scoring method developed by Booth (2006) for the ROCF task, indicates that BN (weighted effect size BN: d= -0.71) have marginally weaker coherence than AN (weighted effect size AN: d= -0.53). People with AN (weighted effect size AN: d= -0.48) have superior detailed processing measured by the GEFT (modified version by Happe´ & Booth, 2008), relative to people with BN (weighted effect size BN: d= -0.35) (see table 1.5) (Roberts et al 2011; Harrison et al 2011; Lopez et al 2008a; Lopez et al 2008b).

Weak central coherence is associated with clinical symptoms such as drive for thinness, bulimia, body dissatisfaction (Sherman et al 2006) and obsessive symptoms (Lopez et al 2008a). Furthermore it is especially dominant in a subgroup (approximately 20%) that has features reflective of autistic spectrum disorder and empathy disorders (Wentz et al 2005).

1.18. 5. Central coherence in eating disorders: recovered

A synthesis of studies in those recovered from the illness indicates that they differ from controls with medium effect sizes on the ROCF (weighted effect size: d= -0.42) and the GEFT task (weighted effect size: d= -0.62) (Tenconi et al 2010; Roberts 2009; Lopez et al 2008b; Pendleton Jones et al 1991) (see table 1.5). Subclinical eating disorder cases (measured by the EAT-40, score>26; Eating Attitudes Test, Garner and Garfinkel, 1989) are also impaired on the ROCF copy and recall subtests (Alvarado-Sanches, Silva-Gutierrez and Salvador-Cruz 2009). It may be proposed that the presence of this trait in those recovered from the illness and its association with subclinical symptoms suggests that weak central coherence is an innate risk factor.

1.18. 6. Central coherence in eating disorders: familial traits

These traits are also present in first degree relatives (unaffected sisters) in comparison to controls with a medium effect size for the ROCF (weighted effect size: d= -0.51) and the GEFT (weighted effect size: d= -0.55) (Tenconi et al 2010; Roberts et al 2011) (See table 1.5).

1.18. 7. Central coherence in eating disorders: biological underpinnings

The biological and genetic basis of weak central coherence has yet to be investigated in eating disorders.

1.18. 8. Central coherence in normal and psychiatric disorders: familial traits

Weak central coherence (measured by the ROCF, Osterrieth 1944), is present in 1st degree relatives of those with schizophrenia (Lee et al 2008), bipolar disorder (Kulkami et al 2010; Frantom et al 2008; Klimes Dougan et al 2006; Gourovitch et al 1999; Doyle et al 2008) ASD (Losh et al 2009; Bolte & Poutska 2006; Baron-Cohen et al 2006; De Jonge, Kemner and van Engeland 2006; Happe, Briskman and Frith 2001; Baron- Cohen & Hammer 1997) and ADHD (Seidman et al 2000).

1.18. 9. Central coherence in normal and psychiatric disorders: biological underpinnings

Genetic factors account for 36% of the variance in performance in control individuals on the Embedded Figures Task (EFT) version that also involves memory abilities (Smalley et al 1989). In ADHD, a heritability estimate of 0.27 for the ROCF was found [using the Bernstein and Waber, (1996) scoring system] (Doyle et al 2008).

Table 1.5: Central Coherence in Those with Current and Recovered Eating Disorders and Their 1st Degree Relatives

	Comparison groups		Test	Findings	Effect size comparison
Current Eating Disorders					
Sherman et al (2006)	AN (n=18)	Controls (n=19)	Rey Central Coherence Index (Savage scoring system 1999)	AN< Controls	(d=-0.87)
Lopez et al (2008a)	AN (n=42)	Controls (n=42)	Rey Central Coherence Index	AN< Controls	(d=-0.93)*
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	Rey Central Coherence Index	ANR< Controls	(d=-0.45)*
				ANBP < Controls	(d=-0.41)
Tenconi et al (2010)	AN (n=153)	Controls (n=120)	Rey Central Coherence index	AN< Controls	(d=-0.47)*
Harrison, Tchanturia and Treasure (2011)	AN (n=50) BN (n=48)	Controls(n=89)	Rey Central Coherence Index	AN < Controls	(d=-0.58)
			Weighted effect size AN, ROCF CCI: d= -0.55 **Weighted effect size AN, ROCF CCI** (scoring method; Booth, 2006) **:** d= -0.53		
Lopez et al (2008c)	BN (n=42)	Controls (n=42)	Rey Central Coherence Index	BN< Controls	(d= -0.57)**
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	Rey Central Coherence Index	BN < Controls	(d=-0.61)**

Harrison, Tchanturia and Treasure (2011)	AN (n=50) BN (n=48)	Controls(n=89)	Rey Central Coherence Index	BN < Controls	(d=-0.88)
			Weighted effect size BN, ROCF CCI (scoring method; Booth, 2006)**:** d= -0.71		
Goddard (2012)	ED Male (n=29) ED Female (n=100)	Control Male (n=42) Control Female (n=90)	Rey Central Coherence Index	ED < HC	
			Weighted effect size EDs (ED + AN + BN), ROCF CCI : d= -0.59 **Weighted effect size EDs (ED + AN + BN), ROCF CCI** (scoring method; Booth, 2006) **:** d= -0.60		
Basseches & Karp (1984)	AN (n=16)	Controls (n=16)	EFT	AN< Controls	(d=-1.02)*
McLaughlin et al (1985)	AN (n=25) BN (n=25)	Controls (n=25)	EFT	AN> Controls	(d=0.84)*
Pendleton-Jones et al (1991)	AN (n=30) BN (n=38)	Controls (n=39)	EFT	AN > Controls	(d=0.72)*
			Weighted effect size AN, EFT: d= 0.39		
McLaughlin et al (1985)	AN (n=25) BN (n=25)	Controls (n=25)	EFT	BN > Controls	(d=1.05)*
Pendleton-Jones et al (1991)	AN (n=30) BN (n=38)	Controls (n=39)	EFT	BN > Controls	(d=0.47)*
			Weighted effect size BN, EFT: d= 0.70		
			Weighted effect size EDs, (AN + BN) EFT: d= 0.53		
Tokley and Kemps (2007)	AN (n=24)	Controls (n=24)	GEFT	AN < Controls	(d=- 0.75)*
Lopez et al (2008a)	AN (n= 42)	Controls (n=42)	GEFT	AN < Controls	(d=-0.50)*

Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	GEFT	AN R< Controls	(d=- 0.41)*
				ANBP < Controls	(d-0.34)*
Harrison, Tchanturia and Treasure (2011)	AN (n=50) BN (n=48)	Controls (n=89)	GEFT	AN < Controls	(d=-0.57)*
			Weighted effect size AN, GEFT: d=-0.48		
Lopez et al (2008c)	BN (n=42)	Controls (n=42)	GEFT	BN < Controls	(d=-0.69)*
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	GEFT	BN = Controls	(d=-0.03)
Harrison, Tchanturia and Treasure (2011)	AN (n=50) BN (n=48)	Controls (n=89)	GEFT	BN <Controls	(d=-0.42)*
			Weighted effect size BN, GEFT: d=-0.35		
Goddard (2012)	ED Male (n=29) ED Female (n=100)	Control Male (n=42) Control Female (n=90)	GEFT	ED = Control * Males < Females * Males ED > Controls * Female ED < Controls *	
			Weighted effect size EDs (AN + BN), GEFT: d= -0.43		

			Recovered		
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	ROCF CCI	Recovered AN = Controls	(d=-0.06)
Tenconi (2010)	Recovered AN (n=29) Weight recovered AN (n=63)	Controls (n=120)	ROCF CCI	Recovered AN< Controls	(d=-0.36)
				Weight Recovered AN < Controls	(d=-0.46)
Harrison, Tchanturia and Treasure (2011)	Recovered AN (n=35)	Controls (n=89)	ROCF CCI	Recovered AN < Controls	(d=-0.67)
			Weighted effect size recovered AN, ROCF CCI : d=-0.40		
Lopez et al (2008b)	Recovered ED (n=42)	Controls (n=42)	ROCF CCI	Recovered ED < Controls	(d=-0.57)*
			Weighted effect size recovered EDs (AN + BN), ROCF CCI : d= -0.42		
Pendleton et al. (1991)	Weight recovered AN (n=20)	Controls (n=39)	EFT	Weight recovered AN > Controls	(d=0.80)*
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non AN sisters (n=30) Non BN sisters (n=20)	Controls (n=88)	GEFT	Recovered AN < Controls	(d=-0.56)*
Harrison, Tchanturia and Treasure (2011)	Recovered AN (n=35)	Controls (n=89)	GEFT	Recovered AN < Controls	(d=-0.41)
			Weighted effect size recovered AN, GEFT : d= -0.48		

Lopez et al (2008b)	Recovered ED (n=42)	Controls (n=42)	GEFT	Recovered ED < Controls	(d=-1.01)*
			Weighted effect size recovered ED, GEFT : d= -0.62		
			1st Degree Relatives		
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	ROCF CCI	Non-AN sisters < Controls	(d=-0.92)*
Tenconi et al (2010)	Non-AN Sisters (n=28)	Controls (n=120)	ROCF CCI	Non-AN sisters = Controls	(d=-0.14)
			Weighted effect size AN 1st degree relatives, ROCF CCI : d= -0.49		
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	ROCF CCI	Non-BN sisters < Controls	(d=-0.58)*
			Weighted effect size ED (AN + BN) 1st degree relatives, ROCF CCI : d= -0.51		
Roberts, Tchanturia and Treasure (2011)	ANR (n=35) ANBP (n=33) BN (n=30) AN rec (n=30) Non-AN sisters (n=30) Non-BN sisters (n=20)	Controls (n=88)	GEFT	Non-AN sisters <Controls	(d=-0.92)*
				Non-BN sisters = Controls	(d=-0.15)
			Weighted effect size ED (AN + BN) 1st degree relatives, GEFT : d=-0.55		

ROCF CCI (Rey complex figure task, central coherence index) (ROCF, Osterrieth 1944)
All studies measuring the ROCF CCI have used the Booth scoring system (2006) which is designed specifically to measure central coherence except Sherman et al 2006 which has used the Savage scoring system (1999) which is designed to assess organisational strategy
GEFT (Group embedded figures test) (Witkin, Oltman, Raskin, and Karp, 2002) (modified version by Happe´ & Booth, 2008),

EFT (Embedded Figures Test) (Witkin, Dyk, Faterson, Goodenough and Karp, 1962)
** = P<0.001
**= P<0.05

1.19. Emotional processing

1.19.1. Definition of emotional processing constructs

Emotional intelligence is a broad concept that refers to the ability to perceive, express, assimilate and regulate emotions (Mayer, Salovey and Caruso, 1999). Most research (Oldershaw et al 2011) into emotional processing in eating disorders has focused on the constructs of emotion regulation and recognition.

Emotion regulation is a mechanism by which we control the experience of emotion by prioritising thinking and monitoring emotions (Mayer, Salovey and Caruso, 1999). There are two main emotion regulation strategies, which use 1) conscious, controlled, or 2) unconscious, automatic processes: 'cognitive reappraisal' and 'emotion suppression'. Cognitive reappraisal, re-frames and accepts the emotion and is associated with positive self-esteem, better emotional experiences, adaptive social interactions (Gross, 2002; Saarni, 1990) and effective emotional coping strategies in response to stress (Tugade and Frederickson, 2002). On the other hand 'emotion suppression' results in increased sympathetic activation, negative emotion and worse interpersonal functioning (Gross 1998; Gross and John 2003; Gross 2002; Campbell-Sills, Barlow, Brown and Hofmann 2006). Other distinct strategies include internalising and externalising. Internalising includes avoidance, rumination and suppression of emotion (Aldao, Nolen-Hoeksema and Schweizer, 2010).

The second construct of particular relevance is emotion recognition. This refers to the ability to label complex emotions (Mayer, Salovey and Caruso, 1999). It involves both the perception of the geometric configuration of facial features in addition to the interpretation of its direct and indirect emotional meaning (Adolphs, 2002).

1.19.2. Neural correlates of emotion constructs

Two interacting neural systems, the ventral and dorsal system are thought to be involved in emotional regulation. The emotional significance of a stimulus is integrated predominantly from the ventral system (amygdala, insula, thalamus and ventral striatum), whereas the dorsal system (dorsal, medial and prefrontal cortex) is involved in regulating these affective states (Phillips et al 2003; Quirk and Beer 2006; Urry et al 2006; Harriri et al 2000, Pessoa et al 2002).

Emotion recognition relies on multiple strategies utilising an array of different brain structures that work together; amygdala, orbitofrontal cortex, anterior cingulate cortex, and ventral striatum (Adolphs, 2002). The amygdala is especially important in the recognition of facial expression and social signalling (Calder, Lawrence and Young, 2001).

1.19.3. Emotional processing constructs in relation to eating disorders symptoms

The clinical features of people with eating disorders suggest that there may be deficits in emotional intelligence underpinning the interpersonal difficulties, poor social and emotional cognition and high levels of anxiety (Schmidt and Treasure 2006). Interpersonal difficulties are common, especially in AN (Goldner et al 1999; Oldershaw et al 2010; Tiller et al 1995; Ward et al 2000; Sunday et al 1996) and are similar to that found in ASD (Zucker et al 2007). Anxiety disorders and social phobia predate the onset in 59 - 88% of cases (Godart et al 2000; Kaye et al 2004). Interpersonal difficulties, especially non assertive styles are predictive of the severity of binge eating (Hartmann et al 2009).

People with eating disorders may have alexithymia and use ineffective strategies to regulate emotion, such as avoidance and suppression (Aldao, Nolen-Hoeksema and Schweizer, 2010). Internalising strategies are used particularly in AN and externalising used more by those with bulimic symptomatology.

1.19.4. Neuropsychological assessment of emotional constructs in eating disorders

Experimental measures of emotional regulation have been assessed through responses in the form of attentional biases to emotional stimuli using the stroop (Ashwin et al 2006) or dot probe (Dandeneau et al 2007) paradigms. Complex emotion recognition has been assessed mainly using the reading the mind in the eyes paradigm (RME) (Baron-Cohen et al 1997).

1.19.5. Emotional constructs in eating disorders: acute state

A systematic review of social and emotional functioning, found anomalies in several domains of these constructs (Oldershaw et al 2011). Sensitivity to threat has been found in all forms of eating disorders (Oldershaw et al 2011; Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c). Specifically there are significant attentional biases to social (d=0.75) and angry threat stimuli (d=1.15) with medium to very large effect sizes (Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c). People with eating disorders also have an attentional bias towards rejecting faces and attentional disengagement from accepting faces (Cardi et al 2011) (See Table 1.6). Interestingly this attention to threat may be a gender related risk factor as it was not present in males with eating disorders (Goddard, 2012).

A synthesis of studies using the RME paradigm (see table 1.6) indicates that people with eating disorders (AN and BN) differ from healthy controls with a medium effect size (weighted effect size: d = -0.51) (Russell et al 2009; Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c; Oldershaw et al 2010). However a recent meta-analysis concluded that people with AN but not BN have difficulties (Oldershaw et al 2011).

1.19.6. Emotional constructs in eating disorders: recovered

Attentional biases to social and angry threat stimuli persist with recovery in eating disorders although in an attenuated form (Harrison et al 2010c; Cardi et al 2012) (See table 1.6). Difficulties in emotion recognition measured by the RME remains in an attenuated form in AN (weighted effect size: d=-0.17) (See Table 1.6) (Harrison et al 2010c; Oldershaw et al 2010).

It can be concluded that emotional regulation difficulties and emotion recognition deficits are possible innate traits that are exacerbated as a secondary consequence of the illness state in AN, although findings remain inconclusive for BN.

1.19.7. Emotional constructs in eating disorders: familial traits

These emotional constructs are yet to be directly investigated in eating disorders as familial traits.

1.19.8. Emotional constructs in eating disorders: biological underpinnings

Research examining event-related potentials in BN in response to emotional face processing has found reduced N2 and increased P3 amplitudes indicating deficits in early automatic classification of emotion that is compensated by increased attentional resources (Kuhnpast et al 2009). In BN there is also a decreased neural response in the precuneus and the right amygdala to facial expressions of disgust and anger (Ashworth et al 2011). In response to intense happy and neutral faces, there is increased right ventral putamen activity in people with eating disorders comorbid for bipolar disorder (Hassel et al 2009).

1.19.9. Emotional constructs in normal and psychiatric disorders: familial traits

Abnormalities in emotional processing have been found in 1st degree relatives of those with major depressive disorder and bipolar disorder, with different patterns of brain activation in the amygdala and medial prefrontal cortex in response to face and emotion stimuli (Monk et al 2008; Young et al., 2002; Suguladze et al 2010).

Also, problems in emotion recognition measured by the RME have been found in 1st degree relatives of those with schizophrenia (effect sizes range from d=-0.12 to -0.8) (de Achaval et al 2009; Ibanez et al 2010), ASD (effect sizes range from d=-1.05 to -1.62) (Losh and Piven 2007; Baron Cohen et al 1997) and alcohol dependence (Hill et al 2007).

1.19.10. Emotional constructs in normal and psychiatric disorders: biological underpinnings

In normal individuals there is evidence that both emotional regulation and emotion recognition are genetically determined. Brain activation patterns (N240 and P300 waves) in response to social stimuli (Ekman and Friesens, 1976 pictures of facial emotion) have a heritability of 42-62% in normal adolescent twins (Anokhin, Golosheykin and Heath 2010). It is possible that abnormalities in serotonin function underpin anomalies in the processing of happy, sad and fear

stimuli since people carrying the short 5-HTTLPR allele have an attentional bias to negative faces (Beevers et al 2009; Fox, Ridgewell and Ashwin 2009). Moreover individuals with the short SLC6A4 allele, have greater amygdala activity in response to faces with a fearful expression (Hariri et al 2002), whereas reduced threat related activity in the right amygdala is associated with an increased density of serotonin 2A receptors in the medial prefrontal cortex (Fisher et al 2009).

Dopamine has also been associated with emotional processing. In an explicit emotional face processing task, individuals with the GG allele of the DRD2 genotype allele had greater DLPFC (dorsolateral pre-frontal cortex) and amygdala activity compared to those with the GT allele (Blasi et al 2009).

Table 1.6: Attentional Biases, Emotional Dysregulation and Emotion Recognition in Current and Recovered Eating Disorders

	Comparison groups		Test	Findings	Effect size comparison
Current ED					
Harrison et al (2009) Harrison et al (2010b) Harrison et al (2010c)	AN (n=50) BN (n=50)	Controls (n=90)	Estroop social attentional bias	ED> Controls	(d=0.75) *
				AN> Controls	(d=0.61) *
				BN > Controls	(d=0.82) *
			Estroop angry threat attentional bias	ED> Controls	(d=1.15) *
				AN > Controls	(d=1.09) *
				BN > Controls	(d=1.09) *
Goddard (2011)	ED Male (n=29) ED Female (n=100)	Control Males (n=42) Control Females (n=90)	Estroop social attentional bias	Males > Females *	
			Estroop angry threat attentional bias	ED > Controls * Females > Males *	
Cardi et al (2012)	EDs (n=46,AN=29, BN =17) Recovered ED (n=22)	Controls n= 50	Dot probe task: attentional bias to rejecting faces	ED > Controls AN=BN	(d=0.52)*
			Dot probe task: attentional disengagement from rejecting faces	ED > Controls AN=BN	(d=0.69)*
			Dot probe task: attentional bias to accepting faces	ED > Controls AN=BN	(d=0.57)*
			Dot probe task: attentional disengagement from accepting faces	ED > Controls AN=BN	(d=0.25)*
Russell et al (2009)	AN (n=22)	Controls (n=22)	RME	AN < Controls	(d=-1.4)
Oldershaw et al (2010)	AN (n=40)	Controls (n=47)	RME	AN= Controls	(d=-0.53)

Harrison et al (2010b), Harrison et al (2010c), Harrison et al (2009)	RAN (n=35) ANBP (n=15) BN (n=50)	Controls (n=90)	RME	ED < Controls	(d=-0.43)*
				AN < Controls	(d=-0.49)*
				BN < Controls	(d=-0.30)*
Goddard (2011)	ED Male (n=29) ED Female (n=100)	Control Males (n=42) Control Females (n=90)	RME	ED < Controls *	
			Weighted effect size ED, RME : d= -0.51 **Weighted effect size AN, RME :** d= -0.60 **Effect size BN, RME :** d= -0.30		
Recovered ED					
Harrison et al (2010c)	Recovered AN (n=35)	Controls (n=90)	Estroop social attentional bias	Recovered AN >Controls	(d=0.28)*
			Estroop angry threat attentional bias	Recovered AN > Controls	(d=0.13)*
Cardi et al (2012)	EDs (n=46; AN=29, BN =17) Recovered ED (n=22)	Controls (n= 50)	Dot probe task: attentional bias to rejecting faces	Recovered ED > Controls	(d=0.28)
			Dot probe task: attentional disengagement from rejecting faces	Recovered ED > Controls	(d=0.42)
			Dot probe task: attentional bias to accepting faces	Recovered ED > Controls	(d=0.36)
			Dot probe task: attentional disengagement from accepting faces	Recovered ED > Controls	(d=0.33)
Oldershaw et al (2010)	Recovered AN (n=24)	Controls (n=47)	RME	Recovered AN = HC	(d=0)

Harrison et al (2010c)	Recovered AN (n=35)	Controls (n=90)	RME	Recovered AN < Controls	(d=-0.27)*
			Weighted effect size recovered AN, RME : d=-0.17		
1st degree relatives of ED					

RME (Reading the mind in the eyes) (Baron–Cohen et al 1997)
Estroop social and angry threat attentional bias (Ashwin et al 2006)
Dot-probe task (Dandeneau et al., 2007)
P<0.001**
P<0.05*

1.20. Reward sensitivity and motivated behaviours

1.20. 1. Definition of reward sensitivity and motivated behaviours

Reward sensitivity defines a responsiveness to reward cues and subsequent positive emotion which arises from engaging in reinforcing behaviours. The Behavioural Inhibition and Behavioural Activation Systems (BIS/BAS) is a theoretical paradigm that describes the physiological mechanisms which underpin reward sensitivity (Gray, 1970, described in section 1.6.3.3). The balance between the approach (or behavioural activation) and avoidance systems (BIS) is modulated by effortful control processes (Claes et al 2010). This determines whether the person exhibits reflective or impulsive behaviours. Variations in psychological traits cause the motivation to approach reward, to differ between individuals.

1.20.2. Neural correlates of reward sensitivity and motivated behaviours

The frontostriatal brain network plays a key role in the balance between effortful, approach and avoidant behaviours. This balance is thought to be modulated by the serotonin and dopamine neurotransmitter systems (Congdon and Canli, 2008; Evenden, 1999; Robbins, 2005; Berridge 2007).

1.20. 3. Reward sensitivity and motivated behaviours in relation to eating disorders symptoms

The premorbid traits and clinical features of eating disorders are suggestive of a variation in approach behaviours across the spectrum. The comorbidity with anxiety is a transdiagnostic feature whereas differences across the eating disorder spectrum are present in reward sensitivity (Harrison et al 2010a). Reduced appetite and feeding difficulties are premorbid features of anorexia nervosa (Jacobi et al 2004). This is in contrast to the premorbid enhanced appetite for food, social contact and other approach behaviours in bulimic disorders (BN and BED) (Mobbs et al 2008; Aldao, Nolen-Hoeksema and Schweizer, 2010; Fischer et al 2003). This abnormality in motivational states may account for the common comorbidity of ADHD with BN (13.3%) (Seitz et al 2011).

Impulsive behaviours (eating, drinking, stealing etc) may result from an externalising maladaptive emotion regulation strategy (Fischer et al 2008). People with these traits have unfavourable outcomes (Fichter et al 2006).

1.20.4. Neuropsychological assessment of reward sensitivity and motivated behaviours in eating disorders

A systematic review of self-report measures to assess sensitivity to reward and punishment found that all eating disorders were more sensitive to punishment in comparison to controls (Harrison et al 2009). However, there are differences across the spectrum with restrictive types being the least sensitive to reward and associated with higher levels of behavioural inhibition and bulimic types being the most sensitive to reward and having higher levels of behavioural

activation (Harrison et al 2009; Bijttebier et al 2009). This pattern of motivation remains after recovery (Harrison, Treasure and Smillie 2010d) and has been found using different assessment measures (Jappe et al 2011).

A variety of experimental tasks have been used to measure these concepts however they all involve other aspects of performance such as attention and learning. The drive for monetary reward has been measured with various forms of gambling tasks such as the Game of Dice task (Brand et al 2007) and the Iowa Gambling task (Bechara et al 1993). In these tasks emotional feedback guides the participant's choice, which then results in reward or loss (Starcke et al 2011). Cognitive inhibitory control has been measured by Stroop and Go No Go tasks.

1.20.5. Reward sensitivity and motivated behaviours in eating disorders: acute state

People with eating disorders perform poorly on both the Iowa Gambling task and the Game of Dice relative to control comparison groups (Brogan, Hevey and Pignatti, 2010; Cavedini et al 2006; Cavedini et al 2004; Tchanturia et al 2007; Boeka and Lokken 2005; Liao et al 2009; Davis et al 2010) (See table 1.7). For the Game of Dice task, different outcome variables are presented across studies, however a synthesis of those which present the Game of Dice net score indicates that people with BN have a lower net score (more risky decision making) in comparison to controls with an overall medium effect size (weighted effect size: d = -0.61) and this is also the case to a lesser degree for the binge purge subtype of anorexia with a small effect size (effect size: d = -0.39). In contrast, restricting AN types have a higher net score, indicating safer decision making in comparison to controls with a small effect size (effect size: d=0.24) (Brand et al 2007; Harrison et al 2011)

Poor performance on the Iowa Gambling task has been associated with a worse outcome for anorexia nervosa (Cavedini et al 2006).

1.20.6. Reward sensitivity and motivated behaviours in eating disorders: recovered

Only one study has investigated decision making in people who have recovered from the illness. Tchanturia et al (2007) found that after recovery people with anorexia nervosa perform normally on the Iowa Gambling task (see table 1.7). This suggests that altered reward sensitivity is related to changes that occur in the acute state.

1.20.7. Reward sensitivity and motivated behaviours in eating disorders: familial traits

The familial risk of altered reward sensitivity is yet to be investigated in 1st degree relatives of those with eating disorders.

1.20.8. Reward sensitivity and motivated behaviours in eating disorders: biological underpinnings

People with AN show less differential activation in the ventral striatum and higher dorsal activation in response to gains and losses in a simple reward task (Wagner et al 2007; Wagner et al 2010; Figee et al 2010).

1.20.9. Reward sensitivity and motivated behaviours in normal and psychiatric disorders: familial traits

Intermediate performance on the Go/Nogo-Task (which measures response inhibition, a related trait of altered reward sensitivity) has been found in unaffected siblings of those with ADHD suggesting that motivational processes and sustained attention are familial traits (Uebel et al 2010).

In control males, familial factors account for 46 - 55% of the variance in DSM- III-R defined symptoms of pathological gambling assessed by a diagnostic interview (Eisen et al 1998). This syndrome is the result of genetic factors as well as experiences shared by the twin pairs during childhood.

1.20.10. Reward sensitivity and motivated behaviours in normal and psychiatric disorders: biological underpinnings

People with the 10 allele of the DAT and the 7 repeat allele of the DRD4 in ADHD are more hyperactive (Carrasco et al 2006; Roman et al 2001; Congdon and Canli, 2008). A meta-analysis has found an association between the 7-repeat allele of the DRD4 and increased risk of ADHD, (Congdon and Canli, 2008; Faraone, Doyle, Mick & Biederman 2001; Li, Sham, Owen and He, 2001).

Brain activation studies have found that healthy individuals with higher behavioural activation (measured by the BAS; Carver and White, 1994) have increased amygdala activation in response to aggressive facial expressions (Beaver et al 2008). Those with higher levels of behavioural inhibition [measured by the behavioural inhibition and activation scales (BIS/BAS scales) (Carver and White, 1994) have increased activation in the dorsal anterior cingulate, a region known to be involved in fear conditioning (Beaver et al 2008; Phelps et al 2004; Garavan et al 2002).

Table 1.7: Decision Making Under Conditions of Risk and Uncertainty in Current and Recovered Eating Disorders and Their 1st Degree Relatives

	Comparison groups		Test	Findings	Effect Size comparison
Current Eating Disorders					
Harrison et al (unpublished data)	ANR (n=22) ANBP (n=11) BN (n=24)	Controls (n=39)	Game of Dice net score	ANR > Controls	(d=0.24)
				BPAN < Controls	(d=-0.39)
				BN < Controls	(d=-0.47)
Brand et al (2007)	BN (n=15)	Controls (n=15)	Game of Dice net score	BN < Controls	(d=-0.9)*
			Disadvantageous choices	BN > Controls	(d=1.29)
			Risky (2 numbers)	BN > Controls	(d=1.1)*
			Safe (4 numbers)	BN < Controls	(d=-0.89)*
			Weighted effect size BN, Net score : d= -0.61 **Effect size ANBP, Net score :** d= -0.39 **effect size ANR, Net score :** d= 0.24		
Svaldi, Brand and Tuschen-Caffier (2009)	BED (n=17)	Overweight Controls (n=18)	Game of Dice net score	BED < Controls *	
			Game of Dice risky choices	BED> Controls	
			Game of Dice safe choices	BED < Controls	
Cavedini et al (2004)	AN (n=59)	Controls (n=82)	Iowa Gambling task net cards from advantageous deck	AN < Control **	
				ANR < Control **	
				ANBP =Controls	
Boeka and Lokken (2005)	BN (n=20)	Controls (n=20)	Iowa Gambling task net cards from advantageous deck	BN < Controls *	
			Iowa Gambling task net cards from advantageous deck in final 50 trials	BN < Controls	(d=0.67)
Cavedini et al (2006)	AN (n=38)	Controls (n=30)	Iowa Gambling task net cards from advantageous deck	AN < Controls **	
Tchanturia et al (2007)	AN (n=29)	Controls (n=29)	Iowa Gambling task net cards from advantageous deck	AN < Controls *	

Liao et al (2009)	BN (n=26) AN (n=29)	Controls (n=51)	Iowa Gambling task net cards from advantageous deck	BN < Controls *	
				AN < Controls **	
Davis et al (2010)	BED and Obese (n=65) Obese (n=73)	Normal weight (n=71)	Iowa Gambling task net cards from advantageous deck	BED < Normal weight *	
				Obese < Normal weight *	
				BED = Obese	
Brogan, Hevey and Pignatti (2010)	AN (n=22) BN (n=17) Obese (n=18)	Controls (n=20)	Iowa Gambling task net cards from advantageous deck	AN < Controls**	
				BN < Controls **	
				Obese < Controls **	
				AN=BN=Obese	
Recovered					
Tchanturia et al (2007)	AN long term recovered (n=14)	Controls (N=29)	Iowa Gambling task net cards from advantageous deck	AN recovered = Controls	
1st degree relatives of ED					

Game of Dice net score (safe choices minus risky choices) (Brand et al 2007)
Iowa Gambling task (Bechara et al 1993).
** = P<0.001
**= P<0.05

1.21. Chapter summary

This review has presented findings which suggest that the risk of developing an eating disorder is increased by obsessive compulsive personality traits, impulsive behaviours and anomalies in set shifting, central coherence, emotional intelligence and motivation related behaviours. Many of these traits have been found to be associated with genes that alter functioning within the serotonin, dopamine and BDNF systems. These traits are also often associated with abnormal patterns of brain activation. Although most are transdiagnostic anomalies, some of these vary between the eating disorder sub-groups. Table 1.8 provides a summary of the aforementioned research by presenting effect sizes for potential risk traits, weighted by the sample size of each study.

Specifically women with AN have problems with set shifting, central coherence and have high levels of inhibition, low approach behaviours, make safe choices in gambling tasks, poor emotional recognition and an attentional bias towards social threat (the latter trait is not present in men with AN). Women with BN and BED are similar albeit they have more approach behaviour with risky choices in gambling tasks and lower levels of inhibition. In some cases where BN has developed after a period of AN, certain behaviours related to approach and reward sensitivity may have been altered and acquired as a consequence of starvation. Many of these features are accentuated in the acute phase of the illness, probably due to the increased imbalance of the monoamine neurotransmitters caused by starvation or abnormal patterns of eating behaviour and depressive or anxious symptomatology.

These traits have been found in various clusters in other forms of psychiatric illness such as schizophrenia, OCD, ASD and anxiety disorders. Therefore they are not exclusively indicative of an eating disorder. One possibility is that the specificity of these traits to eating disorders rests in the concomitant grouping of these traits. Kaye (2008) has proposed that eating disorders (AN and BN) can be characterised by a high level of premorbid anxiety that is intensified during adolescence as a consequence of the hormonal changes and stress that occurs during puberty. Restricting food can become powerfully reinforcing since it reduces the availability of plasma tryptophan, which is a rate-limiting step in the production of 5HT. The reduced functional activity of 5HT is thought to reduce anxiety, which reinforces the restriction of food (Kaye, 2008). Once the eating disorder is triggered, its' symptoms of starvation and binging further disrupt the appetitive mechanisms and neurobiological changes occur which can increase depression and anxiety. This increasingly modifies the anomalies in set shifting, central coherence, emotional intelligence, motivation related behaviours and also prognosis thereby encouraging the illness to take a firm hold, making it difficult to recover.

Continued investigations into the identification of endophenotypes for eating disorders are important for prospective ethiopathogenetic research. Investigations should look to adopting

longitudinal designs to examine whether these traits are premorbid and how these traits contribute to the long term outcome of eating disorders. Molecular genetic studies will also provide insight into which specific genes are risk factors and the genetic commonalities between eating disorders and other psychiatric conditions. Lastly, the application of twin methodology, which is the focus of this thesis will assist in determining the genetic and environmental contributions to these traits, so commonly found in eating disorders.

Table 1.8: Summary Table of Effect Sizes in Current and Recovered Eating Disorders and 1st Degree Relatives

	ED (AN + BN)	AN		BN	Rec AN	Rec ED	1st degree relatives (AN + BN)	1st degree AN relative	1st degree BN relative
Set shifting									
WCST	0.56	0.55		0.54	0.35	--	0.49	0.62	0.18
Brixton	0.57	0.45		0.23	0.33	--	0.01	-0.18	0.39
Central coherence									
ROCF (Booth 2006 scoring method)	-0.60	-0.53		-0.71	-0.40	-0.42	-0.51	-0.49	-0.58
ROCF	-0.59	-0.55		--	--	--	--	--	--
GEFT (Happe & Booth 2008 modified version)	-0.43	-0.48		-0.35	-0.48	-0.62	-0.55	-0.92	-0.15
EFT	0.53	0.39		0.70	0.80	--	--	--	--
Emotional processing									
RME	-0.44	-0.47		-0.30	-0.17	--	--	--	--
Estroop Social	0.75	0.61		0.82	0.28	--	--	--	--
Estroop Angry	1.15	1.09		1.09	0.13	--	--	--	--
Reward sensitivity									
Game of dice	--	**ANR**	**ANBP**	**BN**		--	--	--	--
		0.24	-0.39	-0.61					

This table presents Cohen d effect sizes for comparisons between clinical and control groups. Differences are defined as negligible (≥ 0.15 and <0.15), small (≥ 0.15 and <0.40), moderate (≥ 0.40 and <0.75), large (≥0.75 and <1.10), very large (≥1.10 and <1.45) and huge (≥1.45).
Rec=recovered
WCST [Wisconsin card sorting task, perseverative errors (Heaton et al., 1993)]
Brixton task [errors (Burgess & Shallice, 1997)]
ROCF [Rey Osterrieth complex figure task, central coherence index (Osterrieth 1944)]
GEFT [Group embedded figures test, time taken (Witkin, Oltman, Raskin, and Karp, 2002)]
EFT [Embedded Figures Test (Witkin, Dyk, Faterson, Goodenough and Karp, 1962)]
RME [Reading the mind in the eyes, % accuracy (Baron-Cohen et al 1997)]
Estroop social and angry threat attentional bias [pictorial emotional stroop task (Ashwin et al 2006)]
Game of dice net score [safe choices minus risky choices (Brand et al 2007)]

2. Chapter 2: Genetic Influences on Drive for Thinness, Body Dissatisfaction and Bulimia in a Representative Sample of Twins

2.1. Introduction to the chapter

This chapter is the first experimental study of this thesis and investigates the genetic and environmental contributions to behaviours and psychological traits related to eating disorders in a cohort of twins that are representative of the general population. The application of structural equation modelling techniques to this large cohort of twins allows the specific contribution of genes, shared environment and unique environmental factors to be determined. The findings from this chapter justify the succeeding experimental studies that investigate the genetic basis of neurocognitive and behavioural traits in twins with clinically defined eating disorders.

2.2. Background and development of the study

The eating disorder inventory (EDI; Garner, Olmstead and Polivy 1983) is a widely used and validated self-report questionnaire designed to detect the presence of an eating disorder (Garner, Olmsted, & Polivy, 1983).

The inventory was initially developed for and validated in a sample of females with anorexia and bulimia nervosa to be used as a diagnostic tool. It includes 64 items in total and 8 subscales: 1) drive for thinness, 2) bulimia, 3) body dissatisfaction, 4) ineffectiveness, 5) perfectionism, 6) interpersonal distrust, 7) interoceptive awareness and 8) maturity fears (Garner, Olmsted, & Polivy, 1983). The first three subscales are of particular interest to the present study. 'Drive for thinness', specifically assesses an excessive concern with dieting, a preoccupation with weight and fear of weight gain. The second is 'bulimia', which assesses episodes of eating in binges and impulses to purge. The third is 'body dissatisfaction', which detects a dissatisfaction with physical appearance. Since its' original version there have been two revisions; the EDI-2 (1991) and EDI-3 (2004). The EDI-2 was designed to be administered to males or females, aged 12 and upwards. It has 3 additional subscales comprised of 27 new items: 9) asceticism, 10) impulse regulation and 11) social security. The most recent version is the EDI-3 which has been re-designed to reflect more recent theories of eating disorders. It now comprises 3 items to specifically asses eating disorders and 9 general psychological scales that are related to but not specific to eating disorders. In total the EDI-3 has 6 components to assess: 1) eating disorder risk, 2) ineffectiveness, 3) interpersonal problems, 4) affective problems, 5) over control and 6) general and psychological maladjustment. It may be used in females only, aged 13 -53. Individuals with eating disorders score highly on the subscales - drive for thinness, bulimia and body dissatisfaction, suggesting that they may be endophenotypes (Garner, Olmsted, & Polivy, 1983). However the direction of causality in terms of genetic or environmental factors is unclear. The restriction of food often induces a low mood, which is known to increase feelings of body dissatisfaction (Taylor and Cooper, 1992). In addition bulimic behaviours may be

increased by the cycle of binging and purging which are instigated by long periods of starvation and the disruption of biological processes that coincide (Avena, Long and Hoebal, 2005). Therefore it is of value to examine the genetic and environmental contributions to these traits. The most feasible method of attaining sample sizes large enough to perform such statistical analysis has been to assess twin pairs that are representative of the general population.

The heritability of the EDI subscales has been investigated in various twin cohorts, cultures, sexes and ages (Holland, Sicotte and Treasure 1988; Devlin et al, 2002; Keski-Rahkonen et al. 2005; Raevuori et al, 2006; Rutherford, Mcguffin, Katz and Murray, 1993; Klump, McGue and Lacano, 2000; Baker et al, 2009). To date there have been two studies (Holland, Sicotte and Treasure, 1988; Devlin et al, 2002) assessing the genetic basis of these traits in a clinical sample of females with anorexia nervosa. The first study (Holland, Sicotte and Treasure, 1988) was conducted in 1988 in a UK sample of 25 monozygotic and 25 dizygotic twin pairs where at least one twin had a diagnosis of anorexia nervosa. In monozygotic twins there was a significantly smaller difference within pairs in comparison to dizygotic twins suggesting that the three EDI subscales are heritable (Holland, Sicotte and Treasure 1988). Also a linkage study of anorexia nervosa found drive for thinness to be a significantly useful covariate to delimit the population. This analysis found a cluster of affected sibling pairs with much higher and concordant values. In addition, the use of drive for thinness as an additional covariate provided substantial information for mapping genes and found one close to genome wide significance on chromosome 1 (Devlin et al, 2002).

Large representative samples of twins have been investigated using structural equation modelling techniques to determine the specific contribution of genes and environment. In a UK representative sample of 147 monozygotic and 99 dizygotic female twin pairs aged 18 to 45, additive genetics accounted for 44% of the variance in drive for thinness and 52 % of the variance in body dissatisfaction (Rutherford, Mcguffin, Katz and Murray, 1993). However the absence of confidence intervals and a relatively small sample, limits the conclusions that can be drawn from this study.

In a Finnish twin cohort of 4667 male and female twins aged 22 to 17, additive genetics accounted for 59.4% of the variance in body dissatisfaction (EDI-II) and 51% of the variance in drive for thinness in females. This moderate to high heritability in females was not replicated in men, since these traits were purely accounted for by environmental factors [(drive for thinness: shared environment: 85.3 % and unique environment: 14.7%); body dissatisfaction: shared environment: 86.4% and unique environment: 13.6%)]. It was proposed that the EDI may not address the entire scope of body related attitudes in men (Keski-Rahkonen et al. 2005). These attitudes in men may be better accounted for by measures of muscle dissatisfaction (Raevuori et al, 2006).

In a Swedish twin cohort aged 15 to 17, 246 and 238 monozygotic and 181 and 169 dizygotic female–female and male–male twin pairs respectively, and 366 opposite-sex twin pairs, genetic contributions were more substantial for females in comparison to males. Heritability was estimated at 61% and 20% for drive for thinness, for females and males respectively, 57% and 40% for body dissatisfaction for females and males respectively and 16% and 33% for bulimia, in females and males respectively (Baker, Maes et al 2009).

In the Minnesota twin cohort, differences in heritability across ages were found using a modified version of the EDI-II for adolescent use. In 608, 11 year old and 602, 17 year old female twins, additive genetics accounted for 49% of the variance in body dissatisfaction in 11 year olds and 60% in 17 year old adolescent females (Klump, McGue and Lacano, 2000).

In an Australian twin cohort of 699 females twins aged 12 to 15 years old, genetic factors accounted for 35 % of the variance in body dissatisfaction (Wilsch and Wade, 2009).

Table 2.1: Studies Investigating the Heritability of the Eating Disorder Inventory (Garner, Olmstead and Polivy, 1993)

Study	Sample	EDI version	Group	Body dissatisfaction	Drive for thinness	Bulimia
Holland, Sicotte and Treasure, 1988	25 monozygotic and 25 dizygotic female twin pairs with anorexia nervosa	EDI-I	Females	Significant difference in the mean scores between monozygotic and dizygotic cotwins group suggesting heritability	Significant difference in the mean scores between monozygotic and dizygotic cotwin group suggesting heritability	--
Rutherford, Mcguffin, Katz and Murray, 1993	UK representative sample of 147 monozygotic and 99 dizygotic female twins aged 18 to 45	EDI-II	Females	Additive genetics: 52%	Additive genetics: 44%	--
Keski-Rahkonen et al. 2005	Finnish twin cohort of 4667 males and females aged 22 to 17	EDI-II	Females	Additive genetics: 59.4% Unique environment: 40.7%	Additive genetics: 51% Unique environment: 49%	--
			Males	Additive genetics: 0% Shared environment: 85.3% Unique environment: 14.7%	Additive genetics: 0% Shared environment: 86.4% Unique environment: 13.6%	--
Baker, et al 2009	Swedish twin cohort aged 15 to 17, 246 and 238 monozygotic and 181 and 169 dizygotic female–female and male–male twin pairs, respectively, and 366 opposite-sex twin pairs	EDI-II	Females	Additive genetics: 57% Unique environment: 7% Common environment: 36%	Additive genetics: 61% Unique environment: 1% Common environment: 38 %	Additive genetics: 16% Unique environment: 16% Common environment: 69%
			Males	Additive genetics: 40% Unique environment: 7% Common environment: 53%	Additive genetics: 20% Unique environment: 11% Common environment: 69 %	Additive genetics 33% Unique environment: 0% Common environment: 67%

Klump, McGue and Lacano, 2000	Minnesota twin cohort of 608, 11 year old and 602, 17 year old female twins	Modified version of the EDI for adolescent use	11 year old	Additive genetics: 49% Unique environment: 3% Common environment: 48%	--	--
			17 year old	Additive genetics: 60% Common environment: 40%	--	--
Wilsch and Wade 2009	Australian twin cohort of 699 females twins aged 12 to 15 years old	EDI-II	12 to 15 years old	Additive genetics: 35% Unique environment: 23 % Common environment: 42%	--	--

Studies that have investigated the EDI subscales using twin methodology indicate that differences in heritability exist across ages, sexes and cultures, suggesting that these impact upon the contribution of genes to eating disorder traits. It has also been argued that differences across cultures may occur since the heritability of behavioural traits tends to be greater in permissive environments that allow for greater diversity in comparison to more restrictive environments (Kendler, 2001). Therefore it may prove interesting to investigate the heritability of these subscales in a much larger UK sample, 20 years on from Rutherford and colleagues study (1993).

2.3. Aims

The aim of the current study was to explore the extent to which genetic and environmental factors contribute to the liability of psychological symptoms associated with eating disorders in a representative sample of UK twins. A secondary aim was to explore the influence of age on these psychological symptoms.

2.4. Hypotheses

The main hypothesis was that variance in the three psychological symptoms; drive for thinness, body dissatisfaction and bulimia would be accounted for by substantial genetic influences.

2.4.1. Specific predictions:

According to the previous literature, the following predictions were made:

- Variance in drive for thinness and body dissatisfaction would be accounted for by a larger proportion of genetic influences than bulimia.

2.5. Participants

The data was collected from the St. Thomas UK Twin Registry. This registry was initially started in 1993 to investigate osteoporosis and osteoarthritis in women. The success of these studies encouraged its inclusion of males and expansion to incorporate the Aberdeen Twin Registry and the Institute of Psychiatry Adult Registry. It now comprises a total of 12,000 identical and non-identical twins aged between 16 and 85 from all parts of the United Kingdom. The cohorts' average age is approximately 45 years, predominately female and same sex due to its initial aim to investigate diseases that are more prevalent in women (Spector and Williams 2006). The cohort of twins is no different to the UK singleton population on disease related traits or environmental factors (Andrew et al 2001).

The twins receive questionnaires bi-yearly relating to disease and environmental information and the majority has been clinically assessed in detail for hundreds of phenotypes related to common diseases or intermediate traits. Participation is incentivised by the overall aim of contributing to health research and the opportunity to have a full health check during twin visits, which last between 5 to 6 hours (Spector and Williams 2006).

Research (Wade et al, 2006) suggests that approximately 30% of our sample will have at least one lifetime eating disorder behaviour (i.e. low weight, binge eating, self-induced vomiting, laxative or diuretic use or fasting) to the diagnostic threshold as specified by the Diagnostic and Statistical Manual (DSM) of Mental Disorders. Of this group, around 15% will develop lifetime eating disorders, of which around half will have clinically significant eating disorders (Wade et al. 2006).

2.6. Measures

2.6.1. Zygosity determination: peas in a pod questionnaire (Peeters et al 1998)

In cases where zygosity was not determined by a DNA test, the twin status questionnaire 'peas in a pod' (Peeters et al 1998) was administered to both twins of each pair. The questionnaire includes 7 questions and an algorithm of the responses determines zygosity. The first two questions are used to determine the gender of the twins. The measure includes questions such as 'Were your parents able to tell you apart at school age?'. Twin pairs scoring between 7 and 10 are classed as monozygotic twins and those scoring between 1 and 4 are classed as dizygotic twins. In cases where their scores lie between these (i.e. 5 or 6), question 7 is used as a key determining factor. The questionnaire is approximately 96 -98% accurate in determining zygosity (Peeters et al 1998) (see Appendix 1.1 for the questionnaire).

2.6.2. Eating disorder inventory version 2 (EDI-2) (Garner, 2004)

The EDI-2 is a 96 item self-report inventory, which assesses eating disorder symptoms as well as psychological traits associated with the condition. It has 12 scales in total. In the present study 3 scales were administered to participants which included: 1) drive for thinness, 2) body dissatisfaction and 3) bulimia (see Appendix 1.2). The drive for thinness scale assesses an excessive concern with dieting and weight in addition to the extreme pursuit of losing weight. The body dissatisfaction scale assessed the belief that specific body parts associated with pubertal fatness are too large. The bulimia scale assesses the presence of uncontrollable eating defined as binge eating and the presence of self induced vomiting. The questions are counterbalanced. Participants are required to indicate how often they agree with the statement on a 6 point scale ranging from 'always' to 'never'. In a sample of patients with anorexia nervosa Cronbachs alpha ranged between 0.85 to 0.90 for the 3 scales, indicating good internal consistency (Garner et al, 1983).

2.7. Statistical Analyses

The EDI was scored according to the instructions given in the EDI manual (Garner, 2004). If subjects responded to less than 75% of items, their data was considered missing. Therefore, sample sizes vary across the subscale analyses.

Intraclass correlations for the EDI subscales were calculated for monozygotic and dizygotic twins. The investigation into the genetic effects of disordered eating traits across ages was restricted by the limited sample size of age groups, especially dizygotic twins aged 19 to 30. Therefore structural equation modelling could not be computed. However a Spearman's correlation coefficient was used to explore the relationship between age and eating disorder traits. In addition scatter plots are presented.

2.7.1 Univariate twin model-fitting analyses

According to the classical twin design, sources of variation include additive genetic effects, shared environmental effects, and unique environmental effects (which also includes measurement error). The twin design is based on the principle that monozygotic twins are genetically identical (and share 100% of genes) whereas dizygotic twins share only 50% of their genes. However these assumptions may not always be accurate since biological factors can contribute to genetic differences within monozygotic twin pairs (Bruder et al, 2008).

Structural equation modelling was conducted using the Mx statistical package (Neale, 1997). The three EDI subscales were significantly positively skewed. Transforming the data did not reduce the skew substantially. Therefore the continuous data was converted to ordinal data. Participants scoring above the 75th percentile were categorised as 1 and those scoring less were categorised as 0.

The standard full ACE model fitting analysis determines the phenotypic variance of the three components; additive genetic (a2), shared environment (c2), and non-shared environment (e2). The statistical package fits the full (saturated) ACE model and submodels to the data and reports the Akaike Information Criterion (Akaike, 1974). Three submodels are also fitted; 1) AE model, which explains the phenotypic variance by additive genetics (a2) and non-shared environment (e2) and drops the shared environment (c2) parameter, 2) CE model, which explains the phenotypic variance by shared environment (c2) and non-shared environment (e2) and drops the additive genetic (a2) parameter, 3) E model, which explains the phenotypic variance by the non-shared environment (e2) parameter only, dropping the additive genetic (a2) and shared environment (c2) parameters. These submodels are compared with the aforementioned full ACE model. The best fitting model was chosen on the basis of the AIC value; chi square goodness of fit (i.e. change in chi square test indicates no worsening of fit whilst retaining the fewest parameters) and a lower yielded AIC value (indicating a better balance between parsimony and explanatory power).

2.7.2. Assumptions of the twin model

Twin methodology is based on three assumptions. The first is the 'equal environments assumption', which states that monozygotic and dizygotic twins are equally similar within pairs for their exposure to environmental factors that influence the phenotypes being investigated.

Previous studies of eating disorders suggest that this assumption is not violated (Bulik et al 2000). The second is that the effects of genes are additive. Therefore genetic correlations are 1.0 for monozygotic twins and 0.50 for dizygotic twins. The third assumption is that the traits are not subject to assortative mating (Neale et al. 1998).

2.8. Results

In total 3338 twin persons participated by responding to the questionnaire.

Table 2.2: UK Twin Registry Participants

	Monozygotic twins (n=949 twin pairs)	***Dizygotic twins*** (n=720 twin pairs)
Age	57.1 (13.6) (range: 19-87)	59.5 (10.9) (range: 20-87)
BMI	24.01 (6.39)	25.09 (6.64)

BMI: kg/m
Descriptive statistics: mean and standard deviation in brackets

2.8.1. Descriptive statistics

Table 2.3 presents the means, standard deviations and intraclass correlations for the EDI subscales in monozygotic and dizygotic twin pairs. Overall, the correlations suggest that drive for thinness, body dissatisfaction and bulimia are influenced by genetic factors since monozygotic twins have a higher within pair correlation than dizygotic twins. Furthermore it is of interest to note that the within pair correlations for dizygotic twins are greater than 0, suggesting that some familial factors contribute to the risk of disordered eating.

Table 2.3: Means, Standard Deviations and Intraclass Correlations for Eating Disorder Inventory Subscales

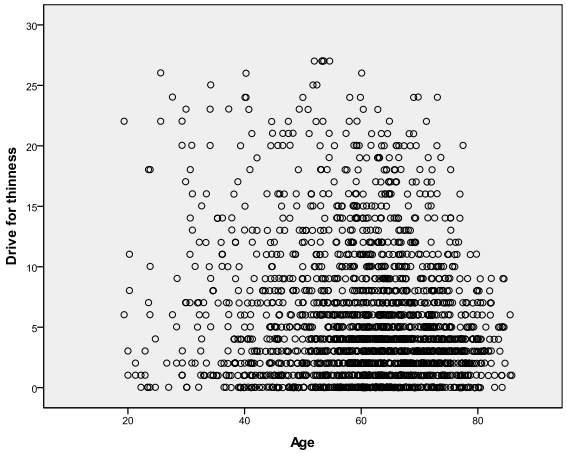
	Monozygotic twins		***Dizygotic twins***	
	Mean (S.D)	*r*	Mean (S.D)	*r*
DT *Total sample (dizygotic n=872, monozygotic n= 1138)*	5.83 (5.71)	0.51 (0.46-0.56) **	5.36 (5.14)	0.20 (0.12-0.28)**
BD *Total sample (dizygotic n=824, monozygotic n=1086)*	15.18 (10.08)	0.55 (0.50-0.60)**	15.63 (9.95)	0.24 (0.16-0.32) **
BN *Total sample (dizygotic n=88, monozygotic n=1167)*	1.69 (2.99)	0.40 (0.33-0.45) **	1.64 (3.04)	0.16 (0.08-0.24) **

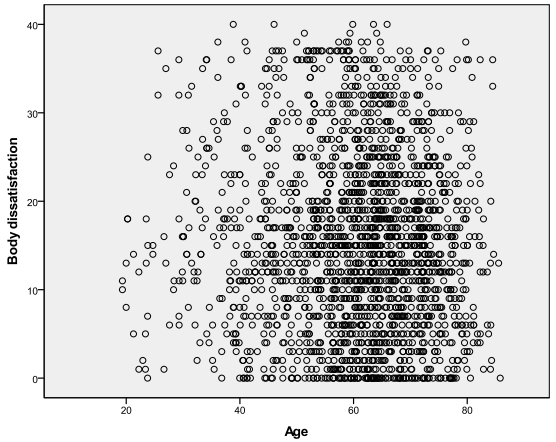
DT: Drive for thinness (Garner, 2004)
BD: Body dissatisfaction (Garner,2004)
BN: Bulimia (Garner,2004)
r :Intraclass correlation coefficients and confidence intervals in brackets
P<0.001**
P<0.05*

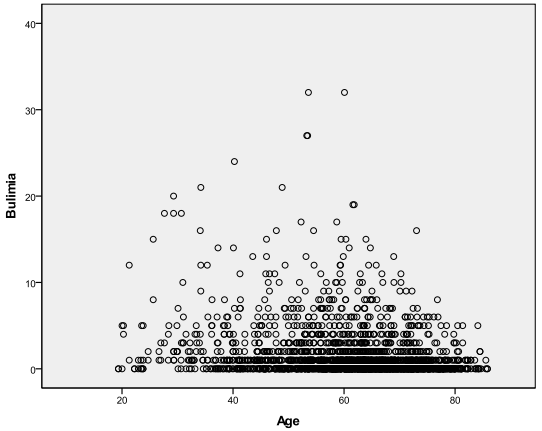
2.8.2. The relationship between age and drive for thinness, body dissatisfaction and bulimia

As age increases, levels of drive for thinness (*r*=-0.13**, p=0.00), body dissatisfaction (*r*=-0.42, p=0.06) and bulimia (*r*=-0.21**, p=0.00) decrease with weak correlation coefficients.

Diagram 2.1: Scatter Plots of Drive for Thinness, Body Dissatisfaction and Bulimia Across Ages







2.8.3 Univariate twin analyses

As can be seen from tables 2.5, 2.7 and 2.9, model fitting analysis indicates that the AE model was the best fit for all three subscales (the traits are influenced by additive genes and unique environmental factors). Heritability was estimated at 60% for drive for thinness, 67% for body dissatisfaction and 52% for bulimia. The traits are also influenced substantially by unique environmental factors which could suggest a large measurement error. Alternatively, this could also indicate a true influence of unique environmental influences. It is not possible to differentiate these.

2.8.4 Model fitting analysis for drive for thinness

Table 2.4: Drive for Thinness

Model	*-2LL*	*Df*	*AIC*	*diffdf*	*diffLL*	*Sig*
ACE	2441.69	2099	1756.31	-	-	-
AE	2441.69	2100	1758.31	1	0	0.1
CE	2458.32	2100	1741.68	1	16.64	0.0
E	2535.77	2101	1666.23	2	94.08	0.0

ACE: Full saturated model with maximum number of parameters.
AE/CE/E: Sub-models
-2LL: -2 times log-likelihood of data
df: Degree of freedom
AIC: Akaike's Index Criterion

2.8.4.1 Drive for thinness results summary

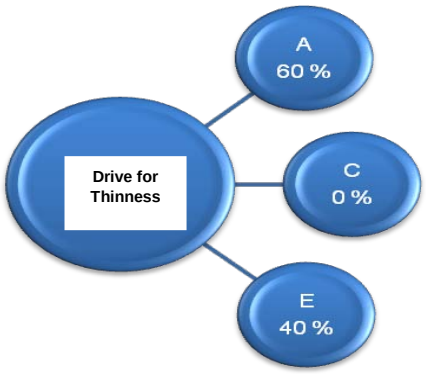
The results indicated that the AE model was the best fitting. This was chosen on the basis of it yielding the lowest AIC value whilst not being significantly different (p=0.1) from the ACE full saturated model. This indicates no worsening of fit whilst retaining the fewest parameters.

Table 2.5: Drive for Thinness ACE Parameter Estimates

	A	*C*	*E*
ACE	0.60	0.0	0.40
AE (best fitting model)	0.60	0.0	0.40
CE	0.0	0.46	0.54

ACE: Additive genetic (a2), non-shared environment (e2) and the shared environment (c2) parameter.
AE: Additive genetic (a2) and non-shared environment (e2) dropping the shared environment (c2) parameter.
CE: Shared environment (c2) and non-shared environment (e2) dropping the additive genetic (a2) parameter.

Diagram 2.2 Pathway Model for Drive for Thinness (AE model)



2.8.5 Model fitting analysis for body dissatisfaction

Table 2.6: Body Dissatisfaction

Model	*-2LL*	*Df*	*AIC*	*diffdf*	*diffLL*	*Sig*
ACE	2230.85	2047	-1863.15	-	-	-
AE	2231.61	2048	-1864.39	1	0.76	0.38
CE	2238.92	2048	-1857.08	1	8.07	0.0
E	2345.34	2049	-1752.66	2	114.49	0.0

ACE: Full saturated model with maximum number of parameters.
AE/CE/E: Sub-models
-2LL: -2 times log-likelihood of data
df: Degree of freedom
AIC: Akaike's Index Criterion

2.8.5.1 Body dissatisfaction results summary

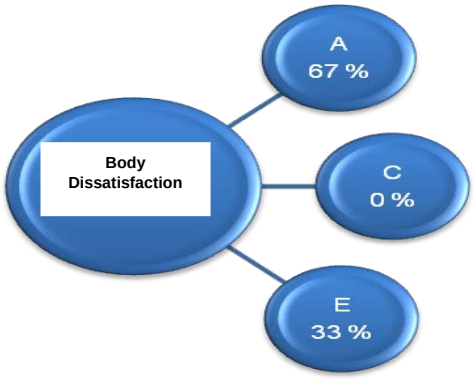
The results indicated that the AE model was the best fitting. This was chosen on the basis of it yielding the lowest AIC value whilst not being significantly different (p=0.38) from the ACE full saturated model. This indicates no worsening of fit whilst retaining the fewest parameters.

Table 2.7 Body Dissatisfaction Parameter Estimates

	A	*C*	*E*
ACE	0.51	0.14	0.35
AE (best fitting model)	0.67	0.0	0.33
CE	0.0	0.55	0.45

ACE: Additive genetic (a2), non-shared environment (e2) and the shared environment (c2) parameter.
AE: Additive genetic (a2) and non-shared environment (e2) dropping the shared environment (c2) parameter.
CE: Shared environment (c2) and non-shared environment (e2) dropping the additive genetic (a2) parameter.

Diagram 2.3 Pathway Model for Body Dissatisfaction (AE model)



2.8.6 Model fitting analysis for bulimia

Table 2.8: Bulimia

Model	*-2LL*	*Df*	*AIC*	*diffdf*	*diffLL*	*Sig*
ACE	2440.79	2117	-1793.21	-	-	-
AE	2440.8	2118	-1795.2	1	0.01	0.92
CE	2447.41	2118	-1788.59	1	6.63	0.01
E	2511.09	2119	-1726.91	2	70.31	0.0

ACE: Full saturated model with maximum number of parameters.
AE/CE/E: Sub-models
-2LL: -2 times log-likelihood of data
df: Degree of freedom
AIC: Akaike's Index Criterion

2.8.6.1. Bulimia results summary

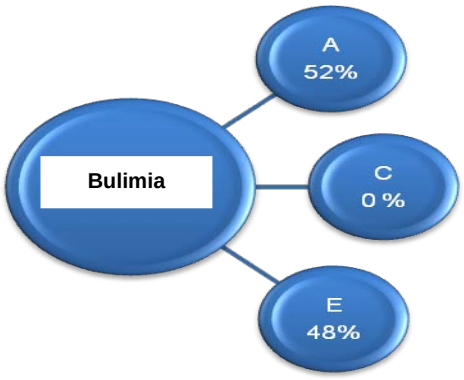
The results indicated that the AE model was the best fitting. This was chosen on the basis of it yielding the lowest AIC value whilst not being significantly different (p=0.92) from the ACE full saturated model. This indicates no worsening of fit whilst retaining the fewest parameters.

Table 2.9 Bulimia Parameter Estimates

	A	*C*	*E*
ACE	0.49	0.02	0.48
AE (best fitting model)	0.52	0.0	0.48
CE	0.0	0.42	0.58

ACE: Additive genetic (a2), non-shared environment (e2) and the shared environment (c2) parameter.
AE: Additive genetic (a2) and non-shared environment (e2) dropping the shared environment (c2) parameter.
CE: Shared environment (c2) and non-shared environment (e2) dropping the additive genetic (a2) parameter.

Diagram 2.4: Pathway Model for Bulimia (AE model)



2.9. Discussion

The present study set out to explore the genetic contributions to the risk of disordered eating in a representative sample of twins in the UK. Substantial genetic influences were found for drive for thinness, body dissatisfaction and bulimia. Furthermore, bulimia was the least influenced by genetics out of the three subscales. There was limited evidence to suggest that age substantially influences these traits.

The influence of genetics to drive for thinness (60%) and body dissatisfaction (67%) were found to be somewhat higher than those found in the UK over 20 years ago (drive for thinness: 44% body dissatisfaction: 52%), in adolescents in Minnesota (47 % for drive for thinness; 49% for body dissatisfaction in 11 year olds and 60% in 17 year olds) and in Finland (51 % for drive for thinness; 59.4% for body dissatisfaction).The greater heritability of these behaviours in our sample may be accounted for by environments (social and cultural aspects) becoming less restrictive with time. For example one study found behaviours such as tobacco use to be more heritable in cohorts where there is less restriction and higher levels of tobacco use (Kendler, Karkowski and Pedersen, 2000). In the Swedish twin cohort (Baker et al 2009) genetic contributions to drive for thinness (61%) were similar to that found in ours, although genetic influences for body dissatisfaction (57%) were lower.

To our knowledge only one other study has estimated the genetic influences of psychological traits associated with bulimia. This study which investigated the Swedish twin cohort estimated 16% heritability for this trait which is considerably lower than that found in the present study (52%) (Baker et al 2009). In our sample environmental influences accounted for 48% of the variance. Environmental factors may include the surge in availability of highly palatable foods in recent times, which may encourage overeating. It may also include the disruption of eating behaviour (fasting, purging) which may encourage changes in behaviour and brain biology that synergistically contribute to bulimic behaviours (Rada et al, 2005; Avena et al, 2005; Boggiano et al, 2007; Boggiano et al, 2005; Avena & Hoebel, 2003; Corwin, 2006; Corwin & Hajnal, 2005). The very different estimates of heritability in our sample in comparison to the Swedish cohort, may also be in part due to the possible existence of different types of individual within both cohorts. Studies have identified two different strains of rat (i.e. ‘binge prone’ and ‘binge resistant’). ‘Binge prone’ rats consume more non-nutritive (junk) palatable foods under conditions of stress, whereas ‘binge resistant’ rats consume less (Boggiano et al 2007).

In the present study all psychological symptoms associated with disordered eating were influenced by genetic factors. Along with previous findings of a genetic contribution to these traits in anorexia nervosa (Holland, Sicotte and Treasure, 1988), it may be seen as clear that there is a substantial genetic component to eating disorder traits in the general population and those with clinically defined eating disorders. This finding justifies the subsequent study (chapter

4) of this thesis, which focuses on the genetic basis of eating disorder symptoms in a clinical sample of twins.

3. Chapter 3: General Methodology for Studies 2 to 7

3.1. Introduction

This chapter outlines the general methodology used in the following studies within this thesis. Descriptions of the twin and familial study designs, recruitment, measures, statistical analysis and participants are provided. These are referred to in the following chapters. Specific descriptions of methodology and samples are presented separately in each respective chapter.

3.2. Studies design

The studies presented in chapters 4 to 9 adopt a cross-sectional case-control study design to compare clinical and control groups across a range of measures. This method was chosen for its increased feasibility and reduced costs in comparison with longitudinal studies.

On the basis of previous research, a set of potential risk traits: 1) childhood obsessive compulsive personality traits, 2) impulsive behaviours, 3) neurocognitive traits, 4) emotional processing styles and 5) reward sensitivity, were chosen to be studied in terms of their endophenotype status. Criteria outlined by Gottesman and Gould (2003) instructed the hypotheses to be tested (chapter 1, section 1.10). To investigate these potential risk traits, familial and twin designs were adopted. Studies 2 to 7 adopt a familial design; people with eating disorders (active and recovered) and their unaffected twin siblings were compared with control twins. The familial design tested the following two endophenotype criteria: 1) the trait is associated with the population (i.e. people with eating disorders) 2) co-segregation with the illness in families and 3) the trait is present in unaffected relatives at a higher level than in the general population (Gottesman and Gould 2003). It is expected that unaffected siblings of those with eating disorders will be behaviourally similar, since they share 50% of genes as well as environmental influences such as parenting styles and culture.

All of the studies within this thesis included twin designs to specifically test the endophenotype criteria of heritability. It was expected that performance would be more similar within monozygotic twin pairs in comparison to dizygotic twin pairs. Since monozygotic twins share on average 100% of genes, any differences within their performances on these tasks are assumed to be due to unique environmental factors. In comparison, differences within dizygotic twins who share on average only 50% of genes, are due to both unique environmental and genetic factors. It is noted that the specified proportion of shared genes within monozygotic and dizygotic twin pairs is merely an approximation since variations will occur due to epigenetic effects.

3.3. Participants

3.3.1. Ascertainment and recruitment

Twin participants were recruited from a variety of sources outlined below.

3.3.2. Ascertainment and recruitment of clinical group

Clinical twin participants were recruited via a newsletter advert from the Department of Twin Research & Genetic Epidemiology King's College London (www.twinsUK.ac.uk). Participants who had taken part in the study by Holland, Treasure and Murray (1988) were also sent a letter of invitation. In addition participants were recruited through an advert placed on our departmental website, www.eatingresearch.com and the eating disorders charity website www.b-eat.co.uk.

3.3.3. Ascertainment and recruitment of control group

Control twin participants were recruited with the help of the Department of Twin Research & Genetic Epidemiology King's College London (www.twinsUK.ac.uk) who sent out a newsletter advert to its twin registry. In addition participants were recruited through adverts placed on our departmental website, www.eatingresearch.com, the eating disorders charity website www.b-eat.co.uk. In addition, adverts were placed in libraries, stores, cafes and shop windows.

3.3.4. Zygosity determination of clinical and control groups

In the clinical group, zygosity was determined by a DNA test for 61.1 % of cases and 90.5% of cases in the control group. For the remaining cases, zygosity was determined by administering the twin status questionnaire 'peas in a pod' to both twins of each pair (described in detail in chapter 2, section 2.6.1) (Peeters et al 1998).

3.4. Demographic and clinical measures

The primary outcome measures were derived from the eating disorder diagnostic interview, neuropsychological and behavioural tasks. Secondary measures included clinical and personality traits that have been associated with the primary measures in previous research. The measures employed within this thesis are provided below.

3.4.1. Demographic questionnaire

A standard form was administered to all participants to obtain demographic details, any personal or family history of psychiatric disorders and general medical history details (see appendix 1.3).

3.4.2. Body mass index

Body Mass Index (kg/m2) was calculated for all participants on the basis of self-report data or objective measurements. The limitations of not obtaining objective height and weight data for all

participant are acknowledged. Research by Meyer, Arcelus and Wright (2009) has indicated that people with eating disorders are relatively accurate in self-reporting their weight. However, women with bulimia nervosa underestimate their weight while women with anorexia nervosa overestimate their weight (Meyer, Arcelus and Wright 2009).

3.4.3. Intelligence quotient (IQ): National adult reading test (NART) (Nelson and Wilson, 1991)
Participants were requested to read a list of non-phonetic words aloud (see appendix 1.4). A higher number of words pronounced incorrectly are indicative of a lower pre-morbid IQ. This estimation of IQ estimation correlates with IQ measured by the British version of the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981) with coefficients ranging from r=0.77 (Crawford et al., 1992) to r=0.81 (Crawford et al, 1989).

3.5. Eating disorder symptoms: diagnosis and screening

3.5.1. The Eating disorder diagnostic scale (EDDS) (Stice, Telch, and Rizvi, 2000)
This 22-item self-report measure is used to identify AN, BN and BED in participants with and without EDs. In the present study it was used to screen for eating disorder pathology within the control sample. The scale has good temporal (*k*=0.80) and criterion reliability (*k*=0.83) with interview diagnosis (see appendix 1.5) (Stice, Telch, and Rizvi, 2000)

3.5.2. Eating disorder inventory version 2 (EDI-2) (Garner, 1991)
The EDI-2 is a 96 item self report inventory which assesses eating disorder symptoms as well as psychological traits associated with the condition (see chapter 2, section 2.6.2. for a full description; appendix 1.2) (Garner, 1991).

3.5.3. EATATE lifetime diagnostic interview (Anderluh et al 2002)
The EATATE semi structured interview (see Appendix 1.6) was administered to participants with an eating disorder and their unaffected twin siblings. It was used to determine current and lifetime eating disorder pathology as well as pre-morbid obsessive compulsive personality traits and lifetime impulsive behaviours. Participants were interviewed by a trained researcher over the phone or face to face. Administration lasted between 45 minutes to 1 hour.

The EATATE was developed by the Healthy Eating Project and is based on well established diagnostic tools. The first of these being the Longitudinal Interval Follow-up Evaluation interview (LIFE: Keller, Lavori, Friedman, Nielsen, Endicott, McDonald-Scott and Andreasen, 1987) which has been used to assess the longitudinal course of psychiatric illnesses in general psychiatry and in eating disorders (Eddy, Dorer, Franko, Tahilani, Thompson-Brenner and Herzog, 2008, Herzog, Sacks, Keller, Lavori, von Ranson and Gray, 1993; Schmidt, Lee, Beecham, Perkins, Treasure, Yi, Winn, Robinson, Murphy, Keville, Johnson-Sabine, Jenkins, Frost, Dodge, Berelowitz and Eisler, 2007). The EATATE is also informed by the Eating Disorder Examination

interview (EDE: Fairburn and Cooper, 1993), which is a validated measure of retrospectively reported and current eating disorders (Fairburn and Cooper, 1993; Ravaldi, Vannacci, Truglia, Zucchi, Mannucci, Rotella, Faravelli and Ricca, 2004). The EATATE instrument has been used previously in research that investigated those with AN (Anderluh et al. 2009) and demonstrates good inter-rater reliability in terms of diagnoses (kappa 0.82–1.0) and illness history variables (0.80–0.99).

3.5.3.1. EATATE part I

Part I of this semi-structured interview assesses the life course of the disorder. It records the body weight and height prior to and during the course of the illness. In addition to menstrual status and BMI it assesses the behavioural and psychopathological symptoms, when they were present, their duration and severity. Behavioural symptoms include; strict dieting, fasting, excessive exercising, binge eating, vomiting, the use of laxatives or diuretics and other compensatory behaviours. Psychopathological symptoms include inappropriate weight concern, fear of food or eating and food preoccupation. For diagnoses the presence of the symptoms are determined by a 3 month duration criteria. The course of each symptom is then plotted on a lifeline, which spans from birth until present. To assist the accuracy of retrospective reporting, participants are probed for anchor points throughout the life course. These include significant life events such as birthdays and courses of treatment etc. Both behavioural and psychopathological symptoms inform the diagnosis that is assigned. The overall lifetime diagnosis is determined by accounting for the diagnoses that has been satisfied across the life course. Each diagnosis is regarded as present if it satisfies a 3 month duration criterion. In the present study, recovery was defined as no reporting of behavioural or psychological symptoms associated with eating disorders for two or more years (Uher et al 2004).

3.5.3.2. Criteria for specific diagnosis

The diagnosis was largely based on DSM-IV (APA, 2000) criteria. Although some changes were applied using recommendations for the new DSM-V, which is due to be delivered in 2013.
For all AN subtypes participants met DSM-IV criteria for:

- A) Refusal to maintain body weight at approximately 85% of that required for height.
- B) Intense fear of gaining weight even though underweight
- C) Disturbance in the way the body, weight or shape is experienced, undue influence of weight on shape or self esteem or denial of the seriousness of their underweight status.

These criteria were assessed using the ‘inappropriate weight concern’ section in the EATATE lifetime interview. The criterion of amenorrhea for AN diagnosis was not required to be present in line with the current diagnostic approaches (Thomas, Vartanian and Brownell, 2009) and recommendations for the DSM-V.

3.5.3.2.1.1 Restricting anorexia nervosa type

The participant must not have engaged in binge eating or purging behaviours, such as self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

3.5.3.2.1.2 Purging anorexia nervosa type

The person has regularly engaged in purging behaviour such as self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

3.5.3.2.1.3 Binge - purge anorexia nervosa type

The person has regularly engaged in binge eating or purging behaviour such as self-induced vomiting or the misuse of laxatives, diuretics, or enemas. Binge eating was determined by the bulimia nervosa criteria A1 and A2 (see below).

Attempting to induce vomiting without success was not counted. When determining lifetime diagnosis, anorexia nervosa purging type was grouped with anorexia nervosa binge purge types.

3.5.3.2.1.4. Bulimia nervosa

Participants were required to meet the criteria for binge eating:

- A1) eating within a discrete period of time (e.g. 2 hours), an amount of food, definitely larger than most people would eat during a similar time/under the same circumstances.
- A2) a loss of control over eating.

These criteria were assessed in the binge eating section of the EATATE interview.
Participants also met criteria for

- B) recurrent inappropriate compensatory behaviours in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas or other medications, fasting or excessive exercise.
- C) In line with proposals for the DSM-V, binge eating and inappropriate compensatory behaviours or purging behaviours were counted if they occurred on average at least once a week for 3 months.
- D) self evaluation is unduly influenced by body shape and weight.
- E) this disturbance does not occur exclusively during periods of anorexia nervosa.

Criteria D and E were assessed using the ‘inappropriate weight concern’ section of the EATATE lifetime interview. The bulimia nervosa diagnosis included the subtypes bulimia nervosa purging type and bulimia nervosa non-purging type which are detailed below.

3.5.3.2.1.5 Bulimia nervosa purging type

The participant will have regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas.

3.5.3.2.1.6. Bulimia nervosa non-purging type

The participant will not have regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or the use of enemas but may have used other inappropriate compensatory behaviours, such as fasting or excessive exercise. When determining lifetime diagnosis, all three bulimia nervosa subtypes were grouped together.

3.5.3.2.1.7. EDNOS

DSM IV EDNOS criteria were used to classify participants who did not meet specific eating disorder criteria.

3.5.3.2.1.8. EDNOS anorexia nervosa

This diagnosis was applied to participants who met the criteria for anorexia nervosa (previously outlined) however despite significant weight loss, the individual's current weight was in the normal range (BMI>18.5).

3.5.3.2.1.9. EDNOS bulimia nervosa

This diagnosis was applied to participants who met the full criteria for bulimia nervosa although binge eating and inappropriate compensatory occurred at a frequency of less than once a week or for a duration of less than 3 months.

3.5.3.2.1.10. EDNOS – inappropriate compensatory behaviours

The participant had engaged in recurrent purging behaviour to influence weight or shape, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, in the absence of binge eating. Self-evaluation is unduly influenced by body shape or weight or there is an intense fear of gaining weight or becoming fat.

3.5.3.2.1.11. EDNOS binge eating disorder

The participant had engaged in recurrent episodes of binge eating (bulimia nervosa criteria A) in the absence of the regular use of inappropriate compensatory behaviours (Bulimia Nervosa criteria B and C). Furthermore sub-threshold binge eating disorder outlined by the DSM-V proposals, was also included whereby binge eating occurs on average, less than once a week.

3.5.3.3. Specific eating disorder lifetime diagnosis

Participants were divided into 6 main lifetime diagnoses (as specified by Anderluh et al 2003) by accounting for the life course of their eating disorder (A full analysis and description of lifetime diagnosis provides the focus of chapter 4). The first group was 'lifetime AN-R type'. The second group was lifetime AN-BP or AN-BP preceded by an episode of AN-R type ' (participants had satisfied a diagnosis of anorexia nervosa restrictive type for at least 1 year or more prior to the development of AN-BP). Participants with EDNOS AN were grouped with 'lifetime AN-R' or 'lifetime AN-BP or with AN-BP preceded by an episode of AN-R' depending on the presence of

binge purge behaviours. The third group was ‘bulimia nervosa with a previous episode of AN’ (participants had satisfied a diagnosis of AN-R type for at least 1 year or more). The fourth group was ‘lifetime bulimia nervosa’. EDNOS-BN was grouped with ‘BN with a previous episode of AN’ or ‘lifetime BN’ depending on whether there was a previous episode of AN. EDNOS binge eating disorder and EDNOS inappropriate compensatory behaviours were categorised separately.

3.5.3.4. Broad eating disorder lifetime diagnosis

Probands were divided into broad eating disorders categories. Those who had a lifetime diagnosis of either, ‘lifetime AN-R type’ or ‘AN-BP or AN-BP preceded by an episode of AN-R’, were placed into the broad ‘AN ’ lifetime group. Those who had a lifetime diagnosis of ‘BN with a previous episode of AN’, ‘lifetime BN’ or EDNOS–BED were placed into the broad ‘bulimic disorders’ (BD) lifetime group. EDNOS inappropriate compensatory behaviours were excluded from the aforementioned broad eating disorder groups.

3.5.3.5. Age of onset

Age of onset was determined by the age at which the participant first met all criteria for the disorder.

3.5.3.6. Duration of illness

Duration of the illness was taken from the age of onset until the age at which the individual no longer satisfied eating disorder criteria.

3.5.3.7. Duration of specific symptoms

Six main clinical variables were derived from the interview: 1) duration of illness (measured in years), 2) duration of excessive exercise (measured in months and recorded if it occurred four times or more per month), 3) duration of fasting (measured in months and recorded if fasting and laxative or diuretic use or vomiting occurred four times or more per month), 4) duration of laxative or diuretic use (measured in months and recorded if laxative or diuretic use and fasting or vomiting occurred once or more per month), 5) duration of vomiting (measured in months and recorded if vomiting and laxative or diuretic use or fasting occurred once or more per month) 6) duration of binge eating (measured in months and recorded if it occurred four times or more per month) and lastly 7) duration of amenorrhea (measured in months).

3.5.4. EATATE interview part II

Part II of the interview (see Appendix 1.7) was used to assess childhood traits reflecting an obsessive compulsive personality that occurred prior to the onset of the eating disorder or before the age of 18. The obsessive compulsive personality traits included perfectionism, inflexibility, rule bound traits, excessive doubt, cautiousness and the need for order and symmetry (see table 3.1). A scoring manual was used to rate all responses according to specific

criteria. Each domain was scored as '2' if the trait overtly impinged on the participant's relationship with the world and with others, '1' if the trait was present but did not overtly affect the participant's life or relationships and 0' if the trait was absent. In the analysis only traits that were scored as 2 were regarded as present.

In addition, the second part of this interview assessed impulsive behaviours that occurred across the lifetime course. Participants were asked whether they had engaged in a total of 12 behaviours such as binge eating, alcohol or substance abuse, self harm, gambling, stealing, disinhibited sexual activity, fire setting, overdosing or spending more money than they felt was sensible. They were probed for feelings of lack of control as an indicator of impulsivity and feelings of regret. Throughout this thesis the total number of impulsive behaviours was analysed with 'binge eating' excluded since this is an eating disorder symptom.

Table 3.1: EATATE Part II: Childhood Obsessive Compulsive Personality Traits

Assessed Traits (Traits were noted if they caused a problem in function)	***Areas of Childs Life***
Perfectionism (Perfectionism was assessed in seven areas of childhood life)	General, school, self-care, looking after their room, pets, hobbies or other.
Inflexibility	Difficulties adjusting to changes such as moving house or, school, changes in family schedule or daily activities. Presence of activities to compensate for inflexibility such as written plans, making contingency plans.
Rule bound	Excessive persistence and high degree of compliance with rules set by parents or teachers.
Excessive doubt and cautiousness (Both needed to be present)	Excessive doubt about actions or excessive cautiousness about making a mistake
Drive for order and symmetry (Present in a minimum of two of the assessed areas)	Looking after their room, housework or appearance (i.e. dress, hair style)

3.6. Co-morbidity measures

Self-report measures were administered to all participants to assess the symptoms that commonly co-occur in eating disorders such as depression (Godart et al 2007) anxiety (Kaye et al 2004) obsessive-compulsive disorders (Crane et al 2007) and low self esteem and typically influence cognitive functioning [Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari and Lönnqvist, (2008), Kuelz, Hohagen and Voderholzer, (2004)]. The self-report measures included the following:

3.6.1. Depression, anxiety and stress scale (DASS)

The DASS is a 21-item questionnaire designed to assess levels of depression, anxiety and stress. The participant is required to rate each item using a 4-point likert scale ranging from 'did not apply to me at all' to 'applied to me very much, or most of the time. The scale results in a

total score, which is the sum of all the items. The scale can be subdivided into three subscales that separately measure levels of depression, anxiety and stress. Items include 'I felt that life was meaningless' and 'I found myself getting agitated'. As a method of screening the control sample, participants were excluded if they scored over the moderate range 20> for depression, 14 >anxiety or 25> stress. The measure has good internal consistency with Cronbachs alpha being 0.96 for depression, 0.89 for anxiety and 0.93 for stress (see appendix 1.8). In this sample Cronbachs alpha was 0.86 for the total score (Lovibond and Lovibond, 1995).

3.6.2. Obsessive-compulsive inventory-revised (OCI-R)

The OCI-R is a revised and shortened version of the OCI (Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002). It assesses obsessive compulsive behaviours. The inventory includes 18 items which participants are asked to rate using a 5-point likert scale ranging from 'Not at all' to 'Extremely'. Items include 'I feel I have to repeat certain numbers' and 'I wash my hands more often and longer than necessary'. The scale results in a total score, which is the sum of all the items. The scale can be divided into six subscales, which assess: washing, checking, ordering, obsessing, hoarding and neutralising. As a method of screening the control sample, participants were excluded if they scored over the clinical cut off 22. The inventory has good internal consistency with the Cronbachs alpha being 0.90 for the total score (see appendix 1.9). In this sample Cronbachs alpha was 0.79 (Foa et al. 2002).

3.6.3. Rosenberg self-esteem scale (RSE)

The RSE is a 10-item measure of self-esteem. Participants are asked to rate each item using a 4 point likert scale ranging from 'strongly agree' to 'strongly disagree'. All 10 items are differentially related to self-esteem and include examples such as 'I feel that I have a number of good qualities' and 'all in all, I am inclined to feel that I am a failure'. The items are counterbalanced with items 2, 5, 6, 8 & 9 being reverse scored. The score is the sum of all the items with a higher scoring indicating a higher self-esteem. This measure has a high internal reliability ranging from 0.77-0.88 (see appendix 1.10). In this sample the Cronbachs alpha was 0.78 (Rosenberg, 1965).

3.7. Personality measures

It was of interest to explore the relationships between personality traits and the primary measures of neurocognitive and behavioural performance. To do this the following measures were used. These are described in detail in their respective chapters:

- Difficulties in emotion regulation scale (DERS) (Gratz and Roemer, 2004) (a full description is provided in chapter 8, section 8.5.5.1).
- Behavioural inhibition system and behavioural activation system scales (BIS/BAS scales; Carver and White, 1994) (a full description is provided in chapter 8, section 8.5.5.2).

- Appetitive motivation scale (AMS Jackson and Smillie, 2004) (a full description provided in chapter 8, section 8.5.5.3).

3.8. Tasks assessing the primary measures of neurocognitive and behavioural performance

The battery included a total of 7 tasks. These measured, set shifting, central coherence, emotional processing and reward sensitivity:

- Two measures of set shifting: (1) Wisconsin Card Sort Task (WCST) (Original manual version by Grant and Berg, 1984, Computerised version (Heaton, Chelune, Talley, Kay, and Curtiss, 1993) and (2) Brixton Task (Burgess and Shallice1997) (full descriptions provided in chapter 7, section 7.5.6)
- Two measures of central coherence: (1) Group Embedded Figures Task (GEFT; Witkin, Oltman, Raskin, & Karp, 2002) and (2) Rey-Osterrieth Complex Figure task (ROCF; Osterrieth 1944) (a full description provided in chapter 7, section 7.5.7)
- Two measures of emotional processing: (1) Reading the Mind in the Eyes Task (Baron-Cohen, Wheelwright, Hill, Raste and Plumb, 2001) and (2) Pictorial Emotional Stroop Task (Ashwin, Wheelwright and Baron-Cohen, 2006) (full descriptions provided in chapter 8, section 8.5.6)
- One measure of altered reward sensitivity: The Game of Dice Task (GDT) (Brand, Fujiwara, Borsutzky, Kalbe, Kessler and Markowitsch 2005a) (a full description provided in chapter 9, section 9.6.2)

3.9. Blinding

It was not impossible to blind the status of each participant since the researcher who collected the data also analysed it. However procedures were taken to minimise the researcher bias in the data collection and scoring of tasks. For example:

- A researcher blind to the participants' ascertainment scored a random selection of 30% of participants. The 2nd scoring of the Rey-Osterrieth Complex Figure Test (described in detail in chapter 7) and NART were assisted by visual (using a camera) and auditory (using a dictaphone) recordings to ensure reliability. There was a high inter-rater agreement between researchers (all higher than: 0.87).
- The EATATE semi-structured interview (see full description in section 3.5.3) determined the eating disorder diagnosis as well as childhood personality traits and lifetime impulsive behaviours (see appendix 1.6 and 1.7). To enable an objective assessment this interview has explicit parameters to score responses and conduct the interview. Participants whose diagnosis required a 2nd opinion were scored by an expert 2nd rater and a conclusion was drawn.

3.10. General description of participants

Participants were divided into different groups dependent on zygosity and clinical status. In total, 114 twins participated. This included 72 twins in the clinical group and 42 control twins. Clinical and control samples were matched for age, sex and levels of intellectual ability.

3.10.1. Clinical group

Zygosity and eating disorder status:

The clinical group consisted of 26 monozygotic twin pairs and 10 dizygotic twin pairs where at least one twin had a history of an eating disorder, aged 17-62 years. Probands in the clinical group were composed of 53 twins with conditions that ranged across the eating disorder spectrum.

In total, 26 probands were categorised as AN on the basis of having conditions involving 'restricted eating': anorexia nervosa restrictive type, anorexia nervosa binge purge type, anorexia nervosa purge type, EDNOS-anorexia nervosa. Twenty six probands were categorised as BD on the basis of having conditions involving 'loss of control over eating': bulimia nervosa, EDNOS-bulimia nervosa, EDNOS-binge eating disorder. One twin pair whose proband had EDNOS inappropriate compensatory behaviours was included in the analysis which compared probands/non-eating disorder cotwins with controls but excluded from the analysis which compared probands/ non-eating disorder cotwins divided by specific diagnoses (i.e. anorexia nervosa and bulimic disorder groups) with controls.

The non-eating disorder cotwins group comprised of 19 twins. This group was then divided on the basis of their probands eating disorder status. There were 12 unaffected twins whose proband was categorised as having a lifetime diagnosis of anorexia nervosa and 6 unaffected twins whose proband was categorised as having a lifetime diagnosis of a bulimic disorder. The non eating-disorder cotwin whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was included in the analysis which compared probands/non-eating disorder cotwins with controls but excluded from the analysis which compared probands/ non-eating disorder cotwins divided by specific diagnoses (i.e. non-anorexia nervosa cotwins and non-bulimic disorder cotwins) with controls.

3.10.1.1. Clinical group: clinical features

The clinical groups are separated on the basis of their zygosity and clinical status (see table 3.2). Although there were no significant differences in demographic details between groups, the probands were somewhat (but not significantly) younger.

- In the probands, 55% (n= 29) began with an episode of restricted eating (anorexia nervosa) and 73.5% (n=39) developed a loss of control over eating (binge eating) during their lifetime. There were no significant differences in clinical features or normal

weight status between monozygotic and dizygotic probands. The number of probands that were currently underweight (BMI< 18.5) were only marginally greater in monozygotic probands (14.6 %) in comparison to the dizygotic probands (0%) group. However monozygotic probands consisted of a larger proportion of those currently ill (i.e. 56.1% recovered) in comparison to dizygotic probands (83.3% recovered). In total only 41.5% (n=22) had received inpatient or outpatient treatment. The probandwise concordance rate for lifetime eating disorder history was 76% in monozygotic twins and 33% in dizygotic twins.

- In the probands, 11.8% (n=6) were currently taking psychotropic medication, furthermore 25.5% (n=13) had been diagnosed with a psychiatric condition throughout their lifetime of which depression was the psychiatric condition for 53.8% (n=7). In the non-eating disorder cotwin group, 5.3 % (n=1) were currently taking psychotropic medication and had been diagnosed with a psychiatric condition (i.e. depression) throughout their lifetime.

Demographics:

- The clinical groups self-defined ethnicity was; 92 % White British, 3% Black British Caribbean and 6 % 'Other White'). English was the first language for all but one set of twins. The twins reported cohabiting with each other for a mean duration of 20.81 years (range: 15-45 years).

3.10.2. Control twin group

Zygosity:

- The control group consisted of 17 monozygotic twin pairs and 4 dizygotic twin pairs, aged 21-61.

Demographics:

- Self-defined ethnicity indicated that the majority (91 %) were White British. English was the first language for all but one set of twins from the clinical group. The twins reported cohabiting with each other for a mean duration of 21.4 years (range: 18-30 years).

Table 3.2: Demographic and Clinical Features for Twins with a Lifetime Eating Disorder Diagnosis and their Cotwins Separated by Zygosity (Monozygotic and Dizygotic) and Controls Twins

	Monozygotic-ED (n=41)	*Monozygotic-H (n=11)*	*Dizygotic-ED (n=12)*	*Dizygotic-H (n=8)*	*Control Twins (n=42)*	**Test statistic**
Age	31 (25)	54 (32)	35 (24.8)	52 (34.5)	45 (22.8)	Wald Chi Square: 6.78, df: 4, p= 0.2
BMI current	20.6 (3.3)	21.9 (7)	21.15 (2.3)	23.65 (4.3)	22.40 (2.2)	--
BMI lowest	16.8 (5.4)	20.1 (3.6)	17.75 (3.5)	19.05 (1.8)	--	--
BMI highest	22 (4.8)	22.3 (6.1)	23.2 (3.7)	24.1 (6.3)	--	--
Age of onset	17 (6)	--	18 (7)	--	--	--
Duration of illness	6 (12)	--	5.25 (8.5)	--	--	--
NART	108 (14)	111.5 (14)	110.5 (15.5)	113 (14.8)	110 (9)	Wald Chi Square: 4.6, df: 4 p= 0.3
Lifetime ED type	AN=48.8% BN= 43.9% EDNOS= 7.3%	--	AN=50% BN= 50%	--	--	--
Recovered	58.1%	--	83.3%	--	--	--
BMI>18.5	85.4%		100%			
Years of Recovery	1 (0-41)	--	8 (0-41)	--	--	--

Monozygotic-ED: Monozygotic eating disorder probands
Monozygotic-H: Monozygotic non-eating disorder cotwin
Dizygotic-ED: Dizygotic eating disorder probands
Dizygotic-H: Dizygotic non-eating disorder cotwin
NART: National adult reading test: IQ estimation
Medians and Interquartile range in brackets.
Years of recovery: Median and range in brackets
Wald Chi Square Test Statistic: Comparison made across all five groups (monozygotic-ED vs. monozygotic-H vs. dizygotic-ED vs. dizygotic-H vs. controls) (1.d.p.)

3.11. Participants inclusion and exclusion criteria:

3.11.1. Clinical group inclusion/exclusion criteria

Twins pairs aged between 16 and 62 where at least one had a lifetime eating disorder history defined by DSM-IV criteria (APA, 2000) (anorexia nervosa, bulimia nervosa, EDNOS-anorexia nervosa or bulimia nervosa types or binge eating disorder) were included. In addition participants with a history of EDNOS-inappropriate compensatory behaviours were included.

Due to the difficulties of recruiting twin participants with current eating disorders, the present study sought to include all twin participants with a lifetime eating disorder history. The probands were in many different phases of the illness and therefore included those who were currently recovered (i.e. had a BMI greater than 18.5) as well as those who were currently ill (BMI<18.5). The exclusion criteria were the presence of epilepsy, neurological conditions, IQ (below 70) [measured by the National Adult Reading Test (NART, Nelson & Wilson, 1991). Depressive and anxious symptomatology was not used as exclusion criteria since this is commonly comorbid in eating disorders (Godart et al 2006)

3.11.2. Control group inclusion/exclusion criteria

Control twins were screened for age (16-62), IQ (above 70) (measured by the NART) and a healthy BMI (between 19-25). They were excluded if there was a personal or family history of psychiatric illness, epilepsy, neurological conditions or head injury. Control twins were also excluded if they scored above the cut-off on one or more self-report measure that screened for the presence of disordered eating behaviour [Eating Disorder Diagnostic Scale (EDDS, Stice et al 2000)], the presence of obsessive compulsive behaviour [Obsessive Compulsive Inventory-Revised, (OCI-R, Foa et al 2002)] and depression, anxiety or stress [Depression Anxiety and Stress Scale; (DASS; Lovibond and Lovibond 1995)].

3.12. Clinical group: co-morbidity and medication

Due to the limited number of twins available to recruit within a specified time frame, the present research did not exclude participants in the clinical group with comorbid psychopathology or those using psychotropic medication. It is acknowledged that these factors influence cognitive performance therefore details of these factors were previously reported in section 3.10.11. Conditions such as depression, anxiety and obsessive compulsive symptoms are frequently comorbid in eating disorders and are known to influence neurocognitive performance and cognitive functioning (Godart et al 2007; Kaye et al 2004; Crane et al 2007; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari and Lönnqvist, 2008, Kuelz, Hohagen and Voderholzer, 2004).

3.13. Ethical considerations

This study was approved by the South London and Maudsley NHS Trust Research Ethics Committee (Study number 09/H0807/67). Participants were given information about the study prior to taking part. Informed consent was obtained on the day of testing. Confidentiality was retained at all stages and participants were allowed to withdraw from the study at any time.

3.14. Session protocol

Participants who volunteered for the project were sent out information regarding their appointment. The researcher booked an appointment time with participants. The appointments were held at the Eating Disorders Research unit at Guys hospital in a quiet and undisturbed assessment room. All participants were compensated £40 for their participation, along with travel costs.

3.14.1. Session protocol for clinical groups

The session began with the participant being given an information sheet to read and consent forms to sign. The experimenter was available to answer questions regarding the study prior to signing the consent forms. Participants were assured that participation was voluntary and that they could leave the experiment at any point. Furthermore rest points were offered throughout the session.

Participants were then administered a battery of neuropsychological and behavioural tasks in the following order: WCST, Estroop, RME task, ROCF task, GEFT task, NART, Game of Dice task and the Brixton task.

Following the assessment, participants were given the self-report measures to complete which lasted up to ½ an hour. After this participants with a current or past eating disorder in addition to their non-eating disorder cotwins were assessed using the EATATE lifetime diagnostic interview for current and lifetime eating disorders and the EATATE part 2 for childhood OCP traits and lifetime impulsive behaviours. The interviews lasted between ½ an hour to 1 ½ hours and were digitally recorded. Permission to record this was granted. Subsequently participants were debriefed. In total each appointment lasted between 3 to 4 hours.

3.14.2. Session protocol for control participants

The session protocol for control participants was the same as that for clinical participants. However interviews were only conducted in cases where the self-report measures indicated that the participant had disordered eating behaviour. In total each appointment lasted between 2 ½ to 4 hours.

3.15. General data analysis

Following the advice of Dr. Daniel Stahl who is a statistician and Lecturer in the Department of Computing and Biostatistics at the Institute of Psychiatry, statistical procedures were applied. The plan for analysis was twofold; utilising both familial (see section 3.15.5.) and twin designs (see section 3.15.6). Unless otherwise specified the following procedures were conducted for each study in chapters 4 to 9.

3.15.1. Statistical power analysis

The measures used in chapter 4 to 9 had not been previously utilised in a twin sample with eating disorders. Therefore due to the exploratory nature of this study a post hoc power analysis was conducted using GPower software. Estimations of the samples sizes needed to detect differences between probands/non-eating disorder cotwins and controls are presented for each measure in the relevant chapter.

Sufficient statistical power to detect group differences was not always attained, due to the limited sample size which resulted from difficulties in recruiting twins with eating disorders. Therefore it was decided to report group differences which had attained a reasonable effect size but had not reached statistical significance. These group differences are reported to occur at 'trend level'.

3.15.2. Inspection of outliers

Outliers were visually inspected using scatter plots of the main outcome variables for each neurocognitive and behavioural task. Outliers were inspected separately for the clinical and control groups. The analysis was conducted with and without outliers excluded. Outliers were identified if they scored 3 standard deviations away from their group mean.

3.15.3. Procedure for assessing the distribution of the data

For each analysis that was planned, data was transformed for outcome measures that were not normally distributed (Gaussian distribution). Distribution of the data was assessed individually for each comparison group. The distribution of the data was determined using a judgment of 3 methods. To begin box plots were visually inspected to assess whether the dispersion of the data was similar across groups. Then QQ plots were also inspected for nonlinear patterns that may indicate a non-normal distribution of the data. Kurtosis and skewness were also taken into account. Lastly, standard deviations were inspected. The outcome of assessing the distribution of the data is presented in the relevant methodology sections. In cases where transforming the data did not reduce the skew of the data, non-parametric methods were used.

3.15.4. Selection of covariates

BMI, age and IQ are potential confounding variables that may influence neuropsychological performance. These variables were considered as candidate covariates. IQ did not differ significantly between groups. However, age did differ between groups at trend level, therefore this variable was used as a covariate in all the parametric analyses.

BMI also differed between groups. A low BMI is a clinical feature that is closely entangled with the symptoms of AN-R, making it difficult to determine how BMI influences neuropsychological function. One study has reported that neuropsychological function (measured by the Trail Making Task- A) is correlated with BMI in patients with AN (Mathias and Kent, 1998). Conversely some studies have found no association between BMI and performance on the Brixton task (Tchanturia et al 2011). Moreover others have found weight recovered patients with AN to persist in having poor set shifting abilities (Tenconi et al 2010).

Since the vast majority of neuropsychological studies (Tchanturia et al 2004; Tchanturia et al 2007) investigating these features have not controlled for BMI it was chosen to concur with this methodology, allowing the present findings to be interpreted within the current evidence base.

Other psychological variables such as depression or anxiety were not used as covariates since these were considered to be comorbid with eating disorder symptomatology.

3.15.5. Statistical analysis using a familial design

To assess familial risk, the clinical group was divided into 'eating disorder probands' (which included monozygotic and dizygotic probands) and 'non-eating disorder cotwins' (which included monozygotic and dizygotic, non-eating disorder cotwins). Non-eating disorder cotwins were separated on the basis of their probands diagnosis into the non-AN cotwins and non-BD cotwins groups. Generalised estimating equations (GEE), an analysis which takes into account the correlative nature of twin pairs was used to conduct the comparisons between probands, non-eating disorder cotwins and controls.

Due to the limited sample size for probands with EDNOS inappropriate compensatory behaviours (n=1), this twin and their non-eating disorder cotwin was excluded from this analysis. Age was used as a covariate throughout. To reduce the risk of a type I statistical error and not limit the ability to detect significant findings, the level of $p<0.05$ was used to report significant results. A correction for multiple testing was not required, since the outcome variables were obtained from a single assessment of each participant.

Cohen's d effect sizes were calculated for each comparison with an effect size calculator, using descriptive statistics that were based on the age covariate. Differences are defined as negligible

(≥ 0.15 and <0.15), small (≥ 0.15 and <0.40), moderate (≥ 0.40 and <0.75), large (≥0.75 and <1.10), very large (≥1.10 and <1.45) and huge (≥1.45).

A descriptive analysis, using means and standard deviations to generate effect sizes, compared performance between probands who were currently underweight with those with a BMI greater than 18.5 (i.e. not underweight).

Spearman's Rho correlation coefficients were used to assess associations between performance on the neurocognitive and behavioural tasks and clinical features in probands, non-ED cotwins and control twins. The duration of clinical symptoms were weighted by age. A bonferroni was used to correct for multiple testing. All analyses were carried out using PASW Statistics version 18.

3.15.6. Statistical analysis using a twin design

The resemblance between monozygotic and dizygotic twin 1 and twin 2 was visually examined using bar charts of the raw outcome variables. The lifetime eating disorder history, underweight and recovered status, are presented in diagrams in chapters 4 to 9. Lines for the control mean and 1 standard deviation away from the control mean were plotted on the graph. Within-pair correlations were calculated for monozygotic and dizygotic twins using intraclass correlation coefficients. These operate on the data structured as twin pairs and describe how strongly twin 1 resembles twin 2.

4. Chapter 4: An Investigation into the Co-Aggregation of Eating Disorders Within Identical and Non-Identical Twin Pairs

4.1 Introduction to the chapter

This chapter describes the second study of this thesis which is aimed at using an in-depth approach to explore how EDs and comorbid conditions such as OCP features and impulsive behaviours co-aggregate within identical and non-identical twin pairs. For this thesis, it is the first step towards investigating the heritability of EDs in a clinical sample. Support for the heritability of EDs within the present sample, merits further exploration of personality, neurocognitive and behavioural traits as heritable risk factors.

4.2 Background and development to the study

As mentioned in the introduction of this thesis (chapter 1) EDs are diagnosed on the basis of the overt symptoms. These diagnostic categories serve to communicate clinical information, choose the most effective intervention and predict prognosis (First et al 2004). However, in practice the assigned diagnosis has not always led to the predicted prognosis due to the frequent fluctuation between categories, over use of the EDNOS category and psychiatric comorbidity (Treasure, Claudino and Zucker, 2010; Eddy et al, 2008; Thomas et al, 2010; Button et al 2005; Walsh and Sysko 2009). Inevitably, this has clinical implications for patients who often want to know their prognosis before entering intensive treatment in inpatient units or undergoing outpatient interventions (Keel and Brown 2010). For these reasons an increased knowledge about the genetic and environmental factors that influence the probable course and outcomes of EDs is an important parameter that requires further insight.

Reviews of longitudinal studies have found similar outcomes in terms of recovery for both AN and BN (Steinhausen and Weber 2009; Steinhausen, 2002). Various factors such as psychiatric comorbidity, have prognostic relevance. The co-segregation of psychiatric conditions within families such as alcohol abuse or avoidant personality disorder have been found to predict a worse outcome in those with BN (Keel and Brown 2010; Clausen, 2008; Bøgh, Rokkedal, Valbak, 2005; Fichter and Quadflieg, 2004). Comorbidities such as OCP features have prognostic relevance for all EDs although especially AN (Anderluh et al 2003; Bardone-cone et al, 2007). For AN, poor prognosis is determined by a greater clinical severity. This may involve a longer duration of illness, a lower desired weight and a higher number of treatment episodes (Keel and Brown 2010; Eisler, Simic, Russel and Dare, 2007; Nisson and Haglofff, 2005; Wentz et al 2009; Fichter, Quadflieg and Hedlund, 2006; Richard, Bauer and Kordy, 2005). Prognostic factors for BED and other EDNOS, include interpersonal factors, sexual abuse and also psychiatric comorbidity (Keel and Brown, 2010; Hillbert et al 2007; Fichter, Quadflieg and Hedlund 2008).

Although psychiatric comorbidity and environmental factors are known to influence prognosis, less is known about whether the course of the eating disorder, in terms of fluctuation between diagnostic categories over time and probability of recovery is genetically determined. Overall it is well known that there exists a substantial genetic basis to eating disorders (anorexia nervosa: 22-62%; bulimia nervosa: 62% and binge eating disorder: 45-56%) (Mazzeo et al 2009; Bulik et al 2006; Bulik et al 2010; Javaras et al 2008; Mitchell et al 2010). It has been suggested that the variability within the broad eating disorder categories (i.e. AN or BN) and the frequent change in symptoms over time may account for the wide range in heritability estimates (Mazzeo et al 2009). This has led to the investigation of the genetic basis of specific symptoms. Perhaps the most recognised phenotype and one which is pertinent to AN, is a low BMI. This physical trait is substantially heritable (Maes et al 1997). However, the individual's intention to lose weight which has been found to be strongly influenced by BMI, is only moderately heritable (38%) and shares relatively little genetic factors with BMI (0.38) (Keski-Rahkonen et al 2005). Similar to the 'intention to lose weight' is dietary restraint and drive for thinness (measured by the EDI, Garner 1991) which appear to be more heritable (44%- 61%) (Castro and Lilenfeld 2005; Rutherford et al 1999; Keskhi Rahkonen et al 2005; Baker et al 2009). Another diagnostic criterion which defines both AN and BN is an intense fear of gaining weight. Similar traits such as 'weight concern at a low weight' have been found to be mainly accounted for by environmental factors, with genetic contributions being limited (0.18-0.29) (Mazzeo et al 2009; Reichborn Kjennerud et al 2004; Wade, Martin Tiggemann, 1998).

Investigations into ED behaviours have shown that those which are easier to objectively define such as bingeing or purging have the greatest genetic causes. Vomiting, which is perhaps the most frequently used purging method is substantially accounted for by genetic factors (53%-72%) (Mazzeo et al 2009; Sullivan, Bulik and Kendler, 1998). In comparison to vomiting, the genetic risk of binge eating varies considerably across studies (28%- 61%) (Wade et al, 2008; Sullivan, Bulik and Kendler, 1998; Reichborn-Kjennuerud et al 2003; Wade et al 2000; Bulik, Sullivan and Kendler, 1998; Klump, et al, 2009; Mazzeo et al 2009). Variability in heritability estimates may be accounted for by differential non-shared environmental factors which can be important in influencing the development of BN, once binge eating has been initiated. These may include early childhood events that are not experienced by the unaffected cotwin, such as abuse or illness or those events that are experienced differently, such as parental expectations (Wade et al 2000).

With this in mind, studies into the genetic and environmental factors that influence prognosis are warranted. Such investigations into the clustering of EDs and related psychiatric co-morbidities within families has great potential to foster our understanding of the aetiology of EDs, inform more precise formulation and effective treatment tailored specifically for EDs (Lilenfeld et al 2006; Bulik et al 2007).

4.3 Aims

The aim of this study was to examine how morbidity co-aggregates within twin pairs with the aim of exploring their heritable nature. To do this a discussion of how these clinical symptoms cluster within MZ and DZ twin pairs will be presented along with diagrams depicting the course of the eating disorder for each twin pair.

4.4 Hypotheses and predictions

Given that eating disorder diagnoses and specific symptoms associated with these conditions are heritable, it was expected that the life course of the eating disorder would also demonstrate a genetic basis. It was expected that MZ twins who share 100% of genes will show greater concordance in terms of, eating disorder type, onset, duration and recovery in comparison to DZ twins who share only 50% of genes.

4.5 Methods

4.5.1. Study design

This study adopted a twin design to compare similarity within MZ and DZ twin pairs for the lifetime course of the eating disorder.

4.5.2 Participants

Participants were the clinical twin group, described in Chapter 3 (section. 3.10). From this sample one concordant MZ twin pair was excluded since they were unable to take part in the present study. They were however assessed using the SCID (structured clinical interview for psychiatric disorders, Spitzer, Williams, Gibbon and First, 1990) and other neurocognitive measures as part of a previous study of sister pairs conducted within our unit. Therefore the present sample included 25 MZ twin pairs and 10 DZ twin pairs where at least one had an eating disorder history as defined by the DSM-IV (APA, 2000).

4.5.3 Measures

The measures used in this study are described in detail in Chapter 3.

In summary, the EATATE part I semi-structured diagnostic interview was administered to the clinical group (probands and non-eating disorder cotwins) to determine lifetime eating disorder diagnosis (Anderluh et al., 2003; section 3.5.3.). Additionally, the EATATE part II interview (section 3.5.4) was administered to the clinical group to determine a history of childhood OCP traits and lifetime impulsive behaviours. The NART (Nelson and Wilson, 1991) was also administered (section 3.4.3).

4.5.5 Data analysis

The symptoms across the different lifetime ED groups are described by medians and inter-quartile ranges (table 4.1). Overall differences in clinical symptoms between the groups are analysed with a Kruskall Wallis test. The participant diagnosed with EDNOS Inappropriate compensatory behaviours was excluded from this analysis due to the limited to sample size.

To examine how morbidity co-aggregates within twin pairs, diagrams were created to depict the life course of the eating disorder for each twin and their cotwin. Each lifeline begins from birth, depicting the age of onset until present day. The lifeline depicts each phase of the eating disorder in a consecutive sequence until their current status, whether that is recovered or currently ill. Parallel to this is their cotwin's lifeline which allows both to be compared. In addition childhood OCP traits and lifetime impulsive behaviours are depicted on each lifeline. Following this, a discussion of ED histories is presented within the context of the current evidence base.

4.6 Results

Demographic and clinical details of the MZ and DZ twins in the clinical group are presented in chapter 3, table 3.2.

4.6.1 The life course of the eating disorders, childhood OCP traits and lifetime impulsive behaviours for MZ and DZ twin pairs

Depicted by diagrams 4.1a, 4.1b and 4.1c are the MZ twin pairs. Twin pairs 1 to 14 (diagrams 4.1a and 4.1b) were concordant for ED diagnosis. The probandwise concordance rate for EDs in MZ twins was 72%.

DZ twins are depicted in diagram 4.2. Twin pairs 1 and 2 were concordant. The probandwise concordance rate for EDs was 33% in DZ twins.

More specifically 48 % (14 twin pairs) of the MZ twin pairs were concordant for their broad lifetime ED diagnosis and only 10% (1 twin pair) of the DZ twin pairs were concordant for their broad lifetime ED diagnosis.

Legend:

Below is a legend whereby the colour shade coincides with the broad ED type or an overweight status. Alongside each diagram, specific legends are given to assist the reader.

Grey – No eating disorder
Green – Recovered
Red/pink shades – AN types
Purple/lilac shades – AN binge or/and purge types
Blue shades- BN types
Orange shades- EDNOS (BED or inappropriate compensatory behaviours)
Any shade with blue shading at the top – Overweight

4.6.1.1. Monozygotic twin pairs lifetime diagnoses diagrams: (Twin pairs 1-25)

Diagram 4.1a: MZ Twin Pairs Lifetime Diagnoses (Twin pairs 1-9)

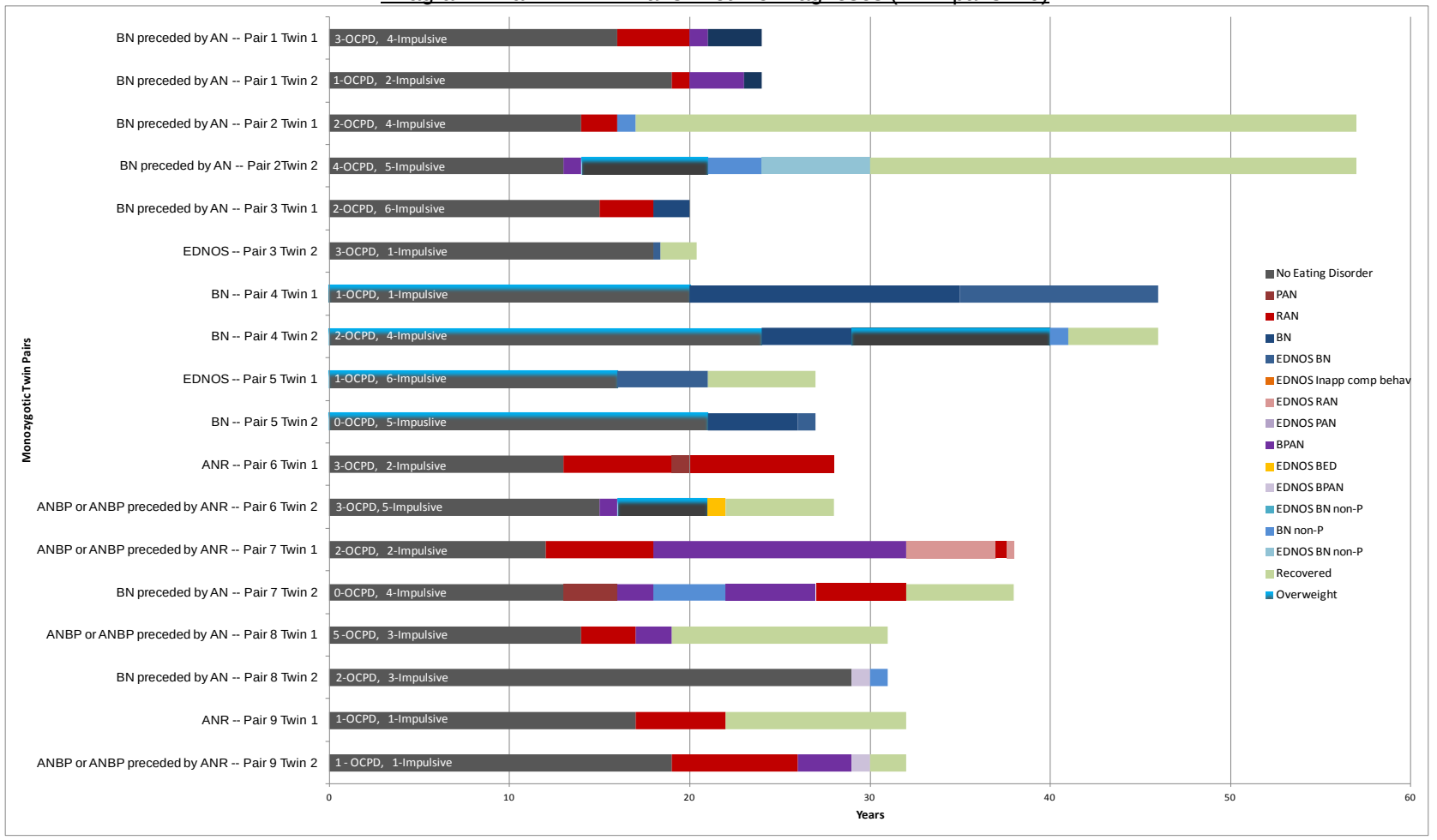


Diagram 4.1b MZ Twin Pairs Lifetime Diagnoses (Twin pairs 10-17)

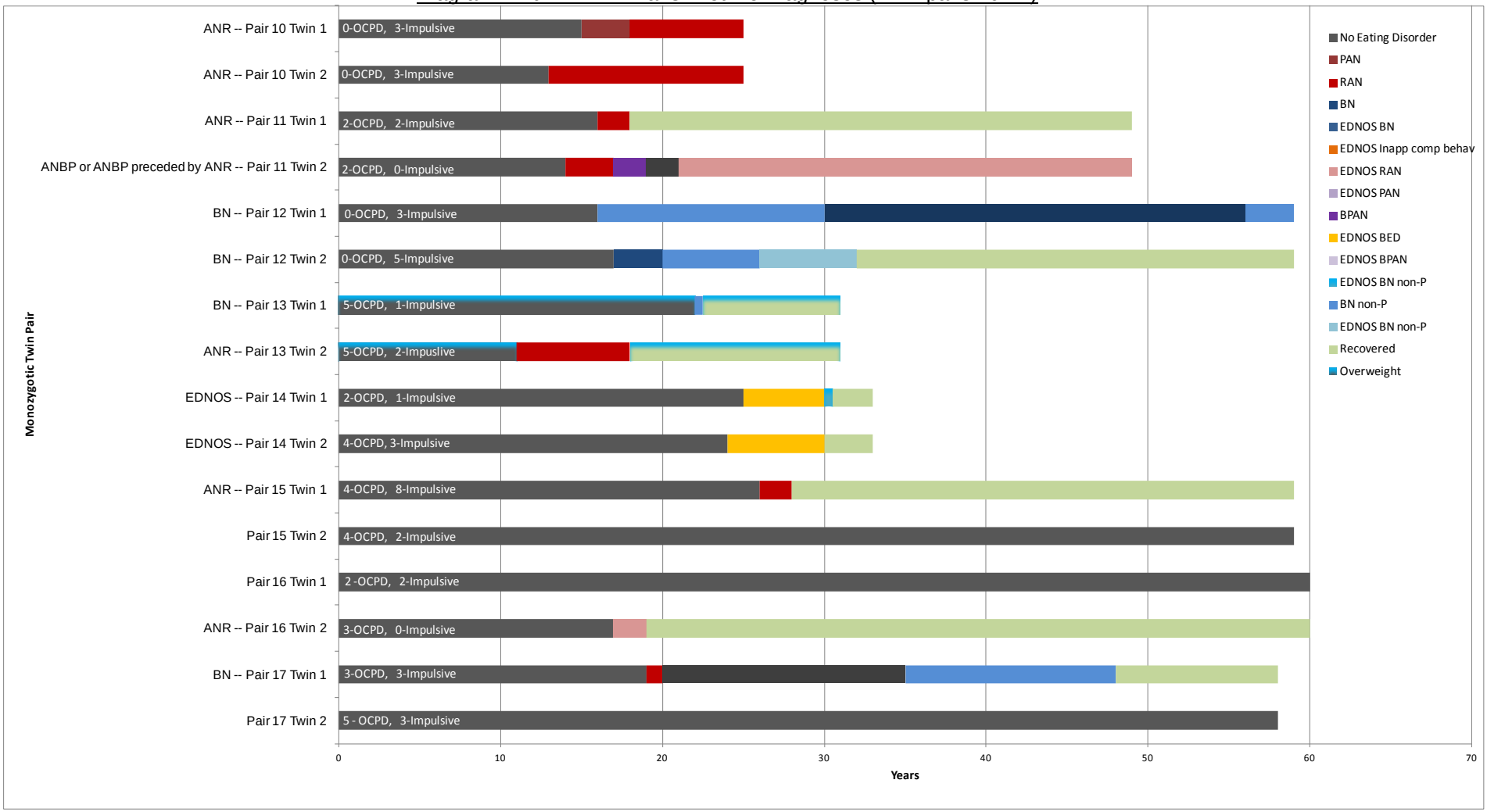
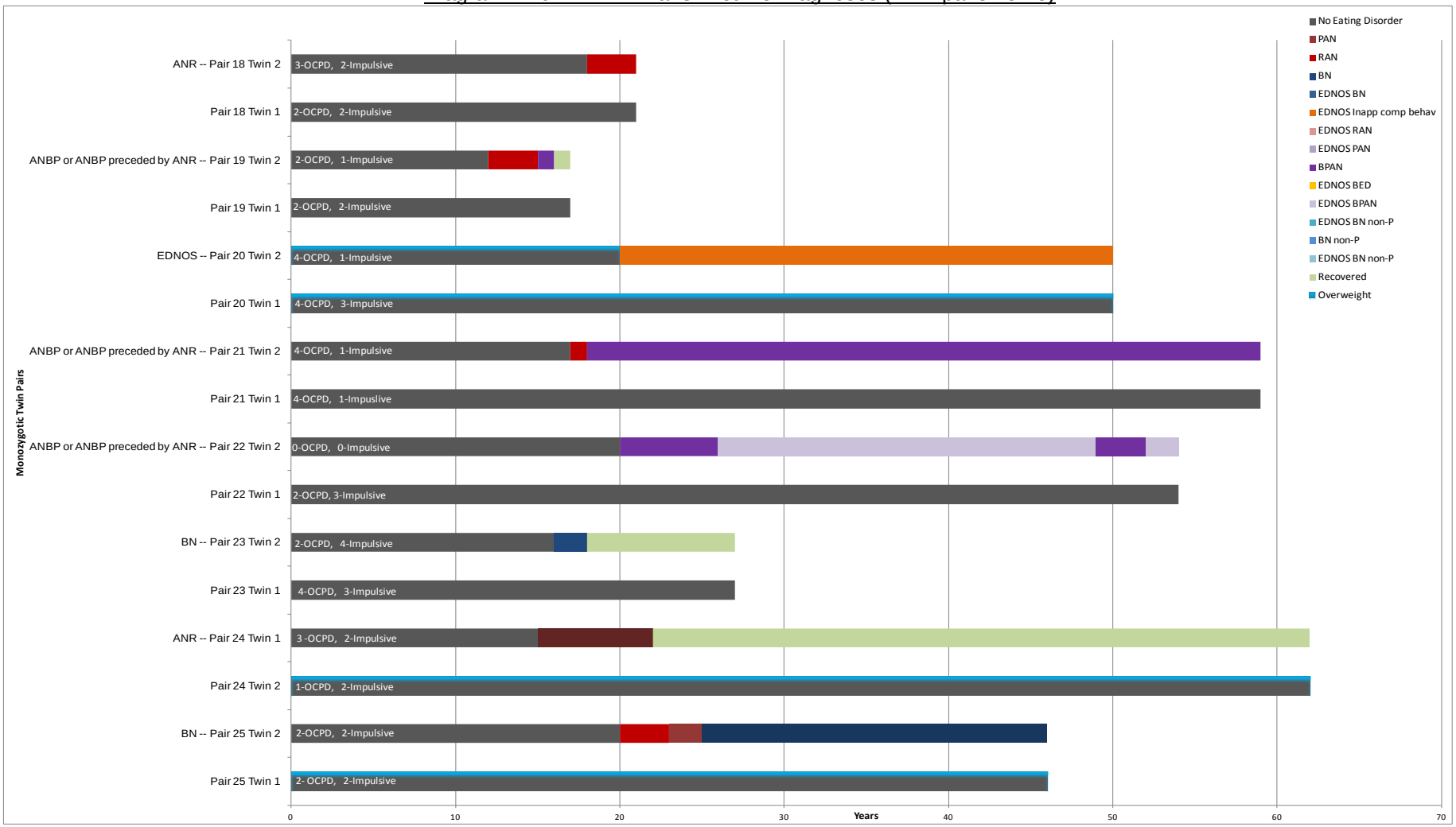
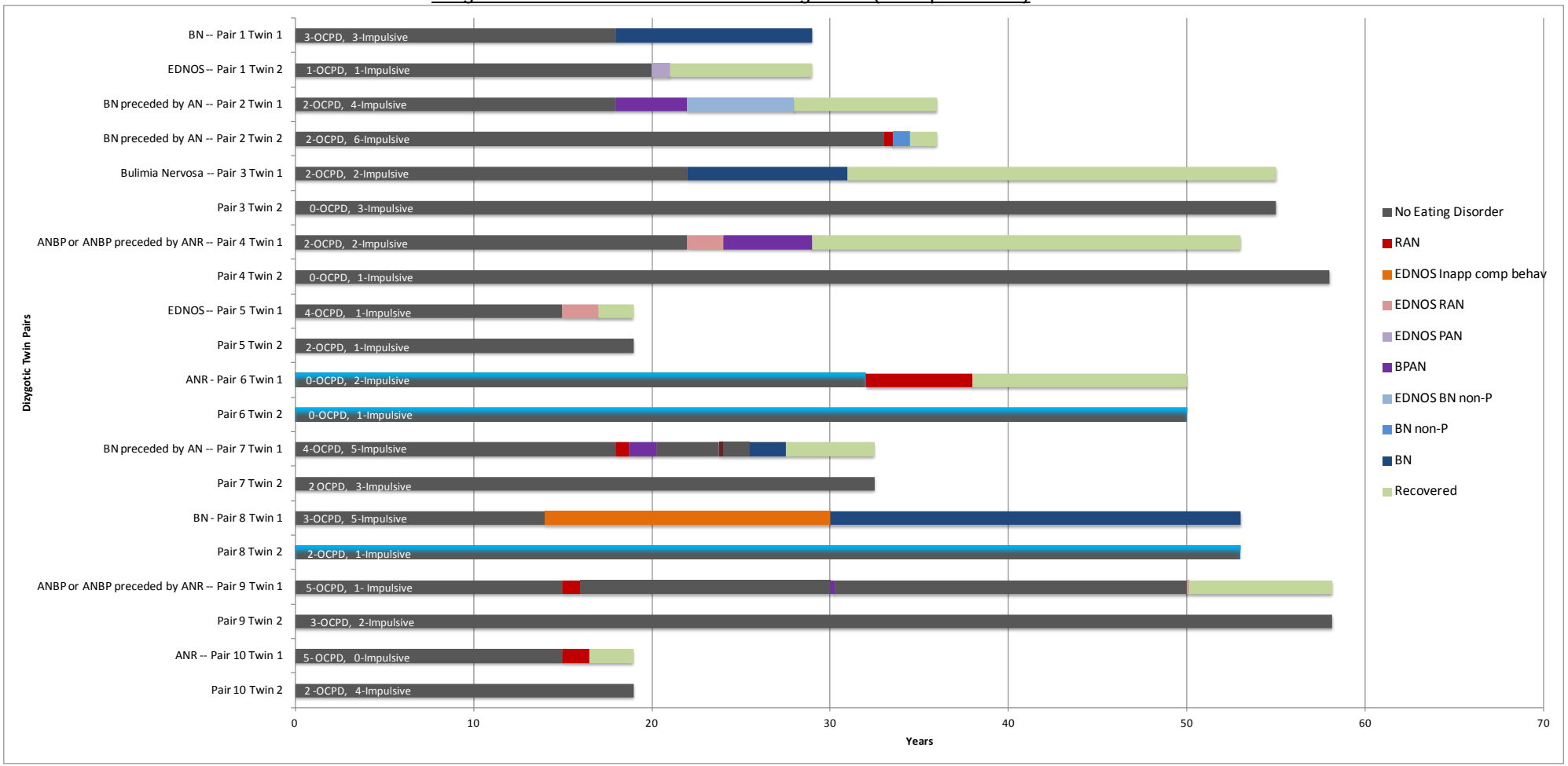


Diagram 4.1c MZ Twin Pairs Lifetime Diagnoses (Twin pairs 18-25)



4.6.1.2. Dizygotic twin pairs lifetime diagnoses diagrams: (Twin pairs 1-10)

Diagram 4.2 DZ Twin Pairs Lifetime Diagnoses (Twin pairs 1-10)



4.6.1.3. Probands lifetime diagnoses and symptoms

Table 4.1: Probands Lifetime Diagnoses and Symptoms

	AN-R (n=14)	*AN-BP or AN-BP preceded by AN-R (n=10)*	*BD (n=26)*	*EDNOS – Inappropriate compensatory behaviours (n=1)*	*Test Statistic*
Age	29.5 (29)	43.5 (28)	35 (25)	50	(H(2) = 1.16 p=0.66
Current BMI	20.1 (6.38)	19.5 (2.5)	23.4 (5.7)	26.4	(H(2) = 8.8 p=0.01
BMI below 17.5 duration *(years)*	2 (6.3)	6.8 (18.3)	0 (3)	0	(H(2) = 1.21 p=0.00
BMI overweight duration *(years)*	0 (0)	0 (0)	0 (2.5)	16	(H(2) = 5.38 p=0.07
Amenorrhea duration *(months)*	30 (122)	60 (132)	4.5 (29)	1	(H(2) = 4.02 p=0.00
Bingeing duration *(months)*	0 (0)	102 (201)	93 (124.5)	0	(H(2) = 8.35 p=0.00
Vomiting duration *(months)*	0 (1.3)	0 (36)	30 (93.3)	0	(H(2) = 3.97 p=0.00
Fasting duration *(months)*	1 (12)	45 (141)	12 (57)	372	(H(2) = 8.82 p=0.01
Dieting duration *(months)*	36 (61.5)	96 (378)	54 (126)	0	(H(2) = 2.50 p=0.29
Excessive exercise duration *(months)*	30 (130)	78 (255)	24 (144)	96	(H(2) = 3.41 p=0.18
Laxative diuretic duration *(months)*	0 (12)	6 (36)	0 (4.8)	0	(H(2) = 1.19 p=0.55
Number of OCP traits	2.5 (3.3)	2.5 (2.3)	2 (2)	4	(H(2) = 0.73 p=0.70
Number of impulsive behaviours	1 (1.3)	2 (2)	4 (2.5)	3	(H(2) = 0.66 p=0.00

Data is not normally distributed; therefore medians and interquartile range in brackets are presented.
AN-R: restrictive anorexia nervosa and EDNOS AN-R
BD: Bulimia nervosa, EDNOS-BN and Binge eating disorder
Test statistic: Kruskall Wallis compared AN-R, BD and AN-BP or AN-BP preceded by AN-R
Proband with EDNOS-inappropriate compensatory behaviours were excluded from the analysis due to the limited sample size

4.7. Discussion: co-aggregation of lifetime eating disorders

This study set out to explore how eating disorders and psychiatric comorbidity co-aggregate within twin pairs across the life course. It adopted an in depth approach to examine the clinical symptoms their severity, duration, risk and maintaining factors such as childhood OCP features and lifetime impulsive behaviours.

Firstly, this study demonstrated a genetic component to eating disorders since the probandwise concordance rate was 72% in MZ twins and only 33% in DZ twins. This supports previous research which has demonstrated the heritability of the eating disorders; AN, BN and BED and specific symptoms related to these (Mazzeo et al 2009; Bulik et al 2006; Bulik et al 2010; Javaras et al 2008; Mitchell et al 2010).

At present, less is known about the genetic determinants of the course that the eating disorder takes over time. This study demonstrated its heritability by adopting an in-depth approach that allowed for the visual comparison of the eating disorder life course within twins pairs and between MZ and DZ twins. Diagrams 4.1a, 4.1b, 4.1c and 4.2 provide visual depictions of the eating disorder life course. In concordant MZ twins pairs (twin pairs 1 to 14 in diagrams 4.1a and 4.1b) there is a striking similarity in age of onset, eating disorder types, movement between diagnostic categories and duration of the eating disorder. In comparison, DZ twins who are concordant (twin pairs 1 to 2 in diagram 4.2) demonstrate less similarity in eating disorder type and onset. These diagrams lend support to the heritability of eating disorder prognosis.

Previously, the variability in heritability estimates of eating disorders has been attributed to the wide heterogeneity within each category and the subtleties in the way in which symptoms are defined (Mazzeo et al 2009). These factors were supported by the evidence drawn from the diagnostic interviews in the current study. For example, whether an individual who reported binging and purging regularly, recalls their BMI being 17.5 or alternatively 19, can make the large difference of them being defined as AN-BP or BN. Furthermore the subjective interpretation of whether the individual considers their eating behaviours to be disordered will also affect diagnosis. It was often the case that the unaffected cotwin reported disordered eating patterns that they did not consider to be abnormal nor did it reach clinical significance. A vivid example is one of an identical unaffected cotwin, who reported fasting on a regular basis for religious purposes, alongside episodes of irregular bingeing. Her proband, who was diagnosed with AN-BP, reported similar but more severe behaviours. Other factors that may indicate disordered eating patterns which do not reach clinical significance is an overweight BMI. Previous research has shown that people who later developed BN were more likely to have been overweight in childhood in comparison to their unaffected sisters (Micali et al 2007). Interestingly in this sample, an overweight status was more prevalent in non-eating disorder cotwins of those with BN and BED (42.9%) in comparison to non-eating disorder AN cotwins

(16.7%). In sum, subtle differences in the presentation of clinical symptoms may account for diagnostic difficulties and the wide variability in heritability estimates across studies.

Other factors that could reduce heritability estimates are non-shared environmental factors including various life events, peer group experiences or sexual abuse. These also include the subjective interpretation of non-shared environment. Due to time constraints, these factors were not studied systematically in the present study (see section 4.7.1). However, there was evidence drawn from the interviews to support previous findings that probands are more likely to subjectively perceive greater insecure parental attachment in comparison to their cotwin (Lehoux and Howe, 2007). Other research has also found that AN probands experience more personal vulnerability traits, sexual abuse and higher parental expectations in comparison to their unaffected siblings (Karwautz et al 2001). The potential effects of non-shared environmental factors on the development of EDs are substantial, since it accounts for 17% to 46% of the variance in heritability estimates (Klump, Wonderlich, Lehoux, Lilenfeld and Bulik, 2002). Evidence drawn from the interviews suggests that environmental factors often amplified what began as disordered eating to the development of an ED reaching clinical significance, whereby it was now used as a coping mechanism.

Conversely, concordance rates within MZ twin pairs may be inflated by the environmental factor of having a twin sibling who is genetically predisposed to be physically identical. Anecdotal evidence from the interview indicated that this had motivated some twins to develop or maintain their ED for longer, as a way of remaining physically identical to their cotwin or competing to be physically superior. Supporting this, onset of the eating disorder occurred within a closer time frame for concordant MZ twin pairs [Mdn=2 years (IQR=3.25)] in comparison to DZ twins [Mdn=10 years (IQR=10]. When interpreting this finding the limited sample size of concordant DZ twins is acknowledged.

The childhood OCP traits and lifetime impulsive behaviours are explored using quantitative analysis in the following chapters, 5 and 6.

4.7.1. Limitations

The study of the genetic basis to the course and outcome of eating disorders was limited in the present study by not having systematically assessed environmental factors from conception to present day. These environmental factors include those that occur pre and post-natally. Early life events that occur in the intrauterine environment and subsequent epigenetic changes are other examples of environmental factors that may influence the propensity for eating disorders. The Barker hypothesis (Barker and Osmond, 1986) proposes that adverse environmental influences such the maternal reporting of stress and malnourishment during pregnancy can have permanent effects on the physiology and metabolism of the fetus. This

causes the epigenetic modification of genes which in turn influence the risk of chronic diseases in adulthood, including eating disorders (De Boo and Harding 2006). Early factors such as a low birth-weight have been linked to the later development of behavioural problems, psychiatric disorders (Hack et al 2004; Indredavik et al 2005) and the development of eating disorders (Micali 2005). Such pre-natal environmental factors may have a greater influence on the propensity for eating disorders and associated traits than a genetic disposition.

The present study had an assessment which lasted up to 4 hours, which meant that an extensive assessment of environmental factors was beyond the scope of the present study. A measure that is recommended for future research is the Oxford Risk Factor Interview for Eating Disorders (ORFI) (Fairburn et al 1997). This measure assesses specific risk factors associated with EDs. It is an investigator based interview which establishes the time line prior to ED onset. Areas investigated by the ORFI include parental EDs, obesity, parental depression, and alcohol and substance dependence. These factors have shown evidence of heritability and influence on prognosis. Work by Field and colleagues (2011) have found that loss of control during episodes of overeating (binge eating) is predictive of adverse outcomes such as drug use, binge drinking frequently and developing high levels of depressive symptoms. It is unclear whether binge eating causes these adverse outcomes or whether binge drinking or eating and substance abuse are used to self medicate depressive symptoms. This uncertainty makes these factors all the more interesting to be investigated using genetically informative samples to determine the causal direction.

4.8. Conclusion

This study aimed to explore how morbidity co-aggregates within twin pairs by providing visual depictions of the life course of the ED, premorbid OCP traits and lifetime impulsive behaviours. A comparison between MZ and DZ twin pairs demonstrated the heritability of the life course of EDs since concordant MZ twins' demonstrated a striking similarity in age of onset, eating disorder types, movement between diagnostic categories and duration of the illness in comparison to DZ twins.

Furthermore subtleties in the way in which symptoms are defined and the patient's subjective interpretation of these, make diagnosis on the basis of physical phenotypes challenging and may contribute to the wide heterogeneity within diagnostic categories. This merits the investigation of implicit phenotypes, such as cognition and emotional processing which provides the focus of studies 7 to 9.

5. Chapter 5: Childhood Obsessive Compulsive Personality Features in Women with Eating Disorders: An Investigation in Twins

5.1. Introduction to the chapter

This chapter describes the third study of this thesis, which explores the familial risk and genetic basis of childhood OCP traits in twins with eating disorders. The traits are investigated in terms of endophenotype criteria as outlined by Gottesman and Gould (2003).

For this thesis, this chapter is the first step towards investigating implicit traits such as personality traits that are not currently included as diagnostic criteria, as potential endophenotypes. Support for this hypothesis merits further investigation of neurocognitive traits such as inefficiencies in set shifting and weak central coherence that are associated with obsessive compulsive symptoms and perfectionism as genetic risk factors.

5.2 Background and development of the study

Personality traits have great potential to inform the taxonomy of EDs. Previous research has indicated that perfectionism and obsessive compulsive traits consistently characterise both AN and BN. Further examinations into how these traits cluster within families will help unravel the aetiology of eating disorders and inform more effective treatment strategies (Bulik et al 2007; Lilenfeld et al 2006).

As mentioned in the introduction to this thesis (chapter 1, section, 1.14.3), the EATATE lifetime diagnostic interview (Anderluh et al 2003) was developed to systematically assess childhood behaviours reflecting an OCP in EDs. This refers to a broad spectrum of at least five traits reflecting an obsessive compulsive personality in childhood as opposed to a psychiatric diagnosis in itself. Research using this instrument has found OCP traits to be elevated in people with eating disorders although especially in AN (Anderluh et al 2003; Halmi et al 2010). Childhood traits reflecting an obsessive compulsive personality are a significant predictor of having a diagnosis of obsessive compulsive personality disorder in adulthood (Anderluh et al 2003). In addition the presence of these behaviours in childhood and adulthood moderates ED symptoms and prognosis (Crane et al 2007; Anderluh et al 2009; Heatherton and Baumeister, 1991; Joiner, Heatherton, Rudd, & Schmidt, 1997; Striegel-Moore et al. 2005).

There is evidence to suggest that environmental and genetic factors play a role in contributing to the development of these behaviours. Environmental precipitants include perinatal factors such as high levels of stress during pregnancy which has been associated with cognitive inflexibility and perfectionism in AN (Favaro and Santonastaso, 2010; Favaro and Santonastaso, 2008). Other research has also confirmed the association between perinatal and postnatal factors and the expression of OCD in adulthood (Vasconcelos et al. 2007).

Investigations into first degree relatives of people with eating disorders and twins indicate that obsessive compulsive behaviours and perfectionism are familial and genetic risk factors (Woodside et al 2004; Lilenfeld et al 1998; Bellodi et al 2004; Wade et al, 2008).

The focus of the present study was to investigate the familial and genetic risk of childhood OCP traits measured by the EATATE lifetime diagnostic interview.

5.3 Aims

The aim of this study was to explore whether childhood OCP traits measured by the EATATE diagnostic interview might be considered as endophenotypes using a genetically sensitive design (a twin study). Three endophenotype criteria outlined by Gottesman & Gould (2003) were investigated: a) the association of obsessive compulsive personality traits with EDs, b) co-segregation within families and c) heritability.

5.4 Hypotheses

The main hypothesis was that people with EDs would have elevated levels of childhood OCP traits and investigations into their twin siblings would indicate that these are familial and genetic risks factors.

5.4.1 Specific objectives and predictions:

According to previous literature, the following objectives and predictions were made:

Firstly, the association between childhood OCP traits and the illness was examined by comparing people with EDs with controls. It was hypothesised that people with EDs would have elevated levels of childhood OCP traits in comparison to controls.

Secondly, to assess co-segregation within families, the presence of these traits in non-eating disorder cotwins were examined. It was hypothesised that non-eating disorder cotwins would show elevated levels of childhood OCP traits in comparison to controls.

Thirdly, differences in childhood OCP traits between AN and BD groups were explored. On the basis of previous research it was hypothesised that AN would have elevated levels of childhood OCP traits in comparison to the BD group (Anderluh et al 2003; Halmi et al 2011).

Fourthly, OCP traits were investigated as predictors of specific ED symptoms in probands. It was hypothesised that higher levels of OCP traits would be associated with more severe and chronic symptoms.

Lastly, heritability was examined by comparing MZ and DZ twins with the expectation that the number of childhood OCP traits would be more similar within MZ twin pairs in comparison to DZ twin pairs.

5.5 Methods

5.5.1 Study design

This study employed a cross sectional case-control study design to compare clinical and control groups. A familial design (chapter 3, section 3.15.5) was employed to assess non-eating disorder cotwins in comparison to controls and lastly a twin design (chapter 3, section 3.15.6) was employed to assess the genetic basis of childhood OCP traits (described in detail in chapter 3).

5.5.2 Participants

Participants were the clinical twin group described in chapter 3 (section 3.10). Data for the control group of singletons used within the present study was obtained with permission from two previously published studies by Anderluh and colleagues (2003; 2009) (see table 5.1).

5.5.3 Measures

The measures used in this study were the same as used in chapter 4 (and described in detail in chapter 3, section 3.5.3).

5.5.4 Data analysis

To compare demographic characteristics such as age and BMI across groups, generalised estimating equations were used (see table 5.1).

To assess childhood OCP traits using a familial design, the clinical group was divided into 'eating disorder probands' (which included MZ and DZ probands) and 'non-eating disorder cotwins' (which included MZ and DZ non-eating disorder cotwins).

For the total number of childhood OCP traits, normality of the data was assessed separately for each comparison between probands, non-eating disorder cotwins and control singletons. Transforming the data did not reduce the skew, therefore the non-parametric method of the Kruskall Wallis test was used to compare all three groups on the total number of OCP traits. The Jonkhere test was used to assess for any significant trends across these groups. The post hoc Mann Whitney U test was used to assess between group comparisons for the total number of OCP traits. Rosenthal's (1991) effect sizes was calculated and converted to Cohen's d using an effect size calculator. Differences are defined as negligible (≥ 0.15 and <0.15), small (≥ 0.15 and

<0.40), moderate (≥ 0.40 and <0.75), large (≥0.75 and <1.10), very large (≥1.10 and <1.45) and huge (≥1.45).

For each specific OCP trait (i.e. perfectionism, inflexibility, rule bound traits and the drive for order and symmetry) the proportion of probands, non-eating disorder cotwins and control singletons scoring 2 is presented (see table 5.2) (for scoring instructions see chapter 3, section 3.5.4). This is also presented for AN and BD probands separately in table 5.4. Due to the binary nature of these specific traits, differences between probands, non-eating disorder cotwins and controls were conducted using the Pearson chi square test and Fishers exact test. For these comparisons the odds ratio is presented. This analysis was also used to examine differences between AN with BD probands.

For probands, the total number of OCP traits and perfectionism were assessed as predictors of the duration of eating disorder symptoms (weighted by age). Spearman's correlation coefficients were conducted and those which reached statistical significance were followed up with linear regressions to assess whether they were significant predictors of ED symptoms. For the linear regressions, age was used as an additional covariate (for the duration of ED symptoms not weighted by age).

Statistical analysis using a twin design was conducted as described in chapter 3, section 3.15.6.

5.5.5. Sample size and power

A post-hoc power analysis was conducted using GPower software which indicated that the present sample would have 100%, 100%, and 100% power for detecting group differences between ED probands, AN probands and BD probands and controls at the 0.05 level for childhood OCP traits (based on Anderluh et al 2003).

5.6. Results

5.6.1 Demographic features of clinical twins and controls

Demographic and clinical details of the groups are presented in table 5.1. The clinical groups (described in chapter 3, section 3.10) are separated on the basis of their zygosity and clinical status. The clinical and control groups were significantly different in age (p=0.00).

Table 5.1: Demographic and Clinical Features for Twins with Eating Disorders, Their Non-Eating Disorder Cotwins and Control Singletons

	MZ-ED (n=41)	*MZ-H (n=11)*	*DZ-ED (n=12)*	*DZ-H (n=8)*	*Control singletons (n=28)*	*Test statistic: clinical groups vs. controls*
Age	32 (28)	54 (32)	35 (24.8)	52 (34.5)	24.5 (3.7)	Wald Chi Squ: 34.24 df: 4. p= 0.00**
BMI current	20.6 (3.5)	21.9 (6.0)	21.2 (2.3)	23.7 (4.3)	22.0 (2.1)	--
BMI lowest	16.9 (5.7)	20.2 (2.7)	17.8 (3.5)	19.1 (1.2)	--	--
BMI highest	22.1 (4.9)	22.3 (6.1)	23.2 (3.7)	24.4 (6.3)	--	--
Age of onset	17 (6)	--	18 (7)	--	--	--
Duration of illness	6 (14)	--	5.3 (8.5)	--	--	--
Lifetime ED type	AN=48.6% BN= 43.2% EDNOS= 8.1%	--	AN=50% BN= 50%	--	--	--
Recovered	64.8%	--	83.3%	--	--	--
BMI>18.5	86.5%	--	100%	--	--	--
Years of Recovery	2 (range: 0-41)	--	8 (range: 0-41)	--	--	--

MZ ED: MZ probands
MZ-H: MZ non-eating disorder cotwin
DZ ED: DZ probands
DZ-H: DZ non-eating disorder cotwin
Statistics reported are: Medians and interquartile ranges in brackets.
Years of recovery: Median and range in brackets.
Test statistic: Generalised estimating equations.
(1.d.p.)

Table 5.2: OCP Traits in Probands, Non-Eating Disorder Cotwins and Control Singletons

	Probands N=51	**Non ED cotwins N=19**	**Control singletons N=28**	**Controls vs. Probands vs. Non-ED cotwins**		**Controls vs. Probands**	**Controls vs. Non-ED cotwins**
	Mdn IQR)	*Mdn IQR)*	*Mdn IQR)*	*Chi Square*	*P value*	*Pos Hoc analysis*	*Pos Hoc analysis*
No. of childhood OCP traits	2, (2)	2, (2)	0, (0.8)	42.32	0.00	Controls< Probands** (d=2.08)	Controls<Non-ED cotwins** (d=1.35)
Childhood perfectionism	64.7%	21.1%	0%	35.00	0.00	Controls< Probands**	Controls< Non-ED cotwins**
Childhood inflexibility	54.9%	21.1%	0%	26.22	0.00	Controls< Probands**	Controls < Non-ED cotwins*
Childhood rule bound	52.9%	21.1%	3.6%	10.92	0.00	Controls< Probands** Odds ratio = 5.1	Controls < Non-ED cotwins** Odds ratio = 6.25
Childhood excessive doubt and cautiousness	52.9%	42.1%	3.6%	19.25	0.00	Controls< Probands** Odds ratio = 30.41	Controls < Non-ED cotwins** Odds ratio = 19.65
Childhood drive for order and symmetry	39.2%	57.9%	17.9%	12.33	0.00	Controls< Probands** Odds ratio = 17.44	Controls = No- ED cotwins Odds ratio = 7.21

- Proband: MZ probands and DZ probands
- Non-ED cotwins: MZ and DZ non-eating disorder cotwins
- Total OCP traits: Kruskall Wallis test to compare overall differences between groups for the total number of OCP traits. Statistics reported are medians, followed by interquartile ranges (IQ) in brackets. Cohen's d effect sizes are presented
  - Post Hoc analysis: Mann Whitney used to compare Probands vs. Controls and Non-ED cotwins vs. Controls.
- Specific OCP traits: The Pearson Chi Square used test to compare overall differences for perfectionism, inflexibility, rule bound, excessive doubt and cautiousness and drive for order and symmetry. Statistics reported are the percentage of participants with the OCP trait. Odd ratios are presented.
  - Post Hoc analysis: Pearson Chi Square test or Fishers Exact Test used to compare Probands vs. Controls and Non-ED cotwins vs. Controls.
- P<0.001**
- P<0.05*

5.6.2 Analysis of childhood obsessive compulsive personality traits as associated with eating disorders and as familial traits

i) Eating disorder twins vs. non-eating disorder cotwins vs. controls

There were significant differences between the probands, non-ED cotwins and controls, for the total number of OCP traits (*H*(2) = 42.94, p= 0.00). The Jonkhere test revealed a significant linear trend across the groups (*J*=2370, *z* = 6.546, *r*= 0.66, p=0.00). In addition perfectionism ($\chi 2$ (2) = 35.00, p=0.00), inflexibility ($\chi 2$ (2) = 26.22, p=0.00), rule bound ($\chi 2$ (2) = 10.92, p=0.00), excessive doubt and cautiousness ($\chi 2$ (2) = 19.81, p=0.00) and order and symmetry ($\chi 2$ (2) = 12.33, p=0.00) all differed across the groups.

ii) Eating disorder twins vs. controls

The total number of OCP traits was found to be significantly higher in the probands (*Mdn= 2*) in comparison to controls with a huge effect size (*Mdn=0, U*=108.4*,* p=0.00, d=2.08). All five of the traits that made up the total number of OCP traits were found at a significantly higher level in probands in comparison to controls. Perfectionism was found to be significantly more prevalent in probands in comparison to controls ($\chi 2$ (1) = 31.12, p=0.00) as was inflexibility ($\chi 2$ (1) = 23.81, p=0.00) and excessive doubt and cautiousness with an odds ratio of 30.41 ($\chi 2$ (1) = 19.26, p=0.00). Rule bound traits were significantly higher in probands in comparison to controls with an odds ratio of 5.1 ($\chi 2$ (1) = 9.23, p=0.00) and so was drive for order and symmetry with an odds ratio of 17.44 ($\chi 2$ (1) = 11.77, p=0.00).

iii) Non-eating disorder cotwins vs. controls

The total number of OCP traits was found to be significantly higher in non-ED cotwins (*Mdn= 2*) in comparison to controls with a small to medium effect size (*Mdn=0, U*=108.5*,* p=0.00, d=1.35). Four out of the five OCP traits were found to be significantly more prevalent in non-ED cotwins in comparison to controls.

Perfectionism was found to be significantly more prevalent in non-ED cotwins in comparison to controls ($\chi 2$ (1) = 6.44, p=0.02) as was inflexibility ($\chi 2$ (1) = 6.44, p=0.02), excessive doubt and cautiousness with an odds ratio of 19.65 ($\chi 2$ (1) = 10.86, p=0.00) and rule bound traits ($\chi 2$ (1) = 8.08, p=0.01) with an odds ratio of 6.25. However drive for order and symmetry was not found to differ between the groups (p=0.14) (odds ratio =7.21).

Table 5.3: OCP Traits in Probands and Non-Eating Disorder Cotwins Separated by Diagnosis

	Restrictive anorexia nervosa	***Anorexia binge purge***	***Bulimia nervosa***	***Binge eating disorders***	***Non-AN cotwin***	***Non-BD cotwin***
	N=14	N=10	N=24	N=2	N=12	N=6
Childhood perfectionism	76.9%	54.4%	62.5%	100%	25%	0%
Childhood inflexibility	53.8%	45.5%	54.2%	100%	8.3%	33.3%
Childhood rule bound	53.8%	63.6	45.8%	50%	50%	66.7%
Childhood excessive doubt and cautiousness	46.2%	81.8%	37.5%	100%	41.7	33.3%
Childhood drive for order and symmetry	38.5%	36.4%	37.5%	50%	33.3%	0%

Non-AN cotwin: Non anorexia nervosa cotwins
Non-BD cotwin: Non bulimic disorder (bulimia nervosa and binge eating disorder) cotwins
Statistics reported are the % of those reporting the OCP trait in childhood (i.e. scoring 2 or above)

5.6.3 Analysis of differences between AN and BD probands for obsessive compulsive personality traits

Table 5.4: OCP Traits in AN and BD Probands

	AN	**BD**	**AN vs. BD**
	N=24	**N=26**	
	Mdn IQR)	*Mdn IQR)*	*Chi square*
No. of childhood OCP traits	2, (2)	2, (2.5)	AN = BD Cohen's D =0.14
Childhood perfectionism	64%	68%	AN= BD Odds ratio= 0.94
Childhood inflexibility	52%	56%	AN= BD Odds ratio= 0.93
Childhood rule bound	60%	44%	AN= BD Odds ratio= 1.36
Childhood excessive doubt and cautiousness	64%	40%	AN= BD Odds ratio= 1.6
Childhood drive for order and symmetry	36%	40%	AN= BD Odds ratio= 0.90

AN: MZ and DZ anorexia nervosa probands
BD: MZ and DZ probands bulimic disorder probands (bulimia nervosa and binge eating disorders)
Statistics reported are:

- Medians, followed by interquartile ranges (IQ) in brackets for the total number of OCP traits.
- The percentage of probands with each specific OCP trait.

Statistical tests are:

- Mann Whitney U test for comparing AN vs. BD for the total number of OCP traits. Cohen's d presented.
- Pearson Chi Square test or Fishers exact test for comparing AN vs. BD for perfectionism, inflexibility, rule bound traits, excessive doubt and cautiousness and drive for order and symmetry. Odds ratio presented.

P<0.001**
P<0.05*

5.6.3.1. OCP traits in anorexic and bulimic disorders

i) AN vs. BD

Overall there were no significant differences between AN and BD probands for the total number of OCP traits (U=289, p=0.64) and only a negligible effect sized difference (d=0.13) between these groups. Attention is drawn to two twin pairs, one being discordant for EDNOS inappropriate compensatory behaviours (chapter 4, Diagram 4.1c, twin pair 20) and the other being concordant for BED (chapter 4, Diagram 4.1b, twin pair 14). Both of these pairs reported much higher levels of childhood OCP traits putting them in the 74th percentile of this sample.

No significant differences were found between AN and BD probands for the specific traits: perfectionism ($\chi 2$ (1) = 0.09, p=0.77), order and symmetry ($\chi 2$ (1) = 0.09, p=0.77) rule bound traits ($\chi 2$ (1) = 1.28, p=0.26), inflexibility ($\chi 2$ (1) = 0.08 p=0.77) or excessive doubt and cautiousness ($\chi 2$ (1) = 2.89 p=0.09). This finding may be in part due to lacking statistical power as a consequence of a limited sample size. However a review of the odds ratios comparing these groups indicates that AN probands were more likely to report excessive doubt and cautiousness and rule bounds traits at trend level (see table 5.4) in comparison to BD probands.

5.6.4 Childhood OCP traits as predictors of eating disorder symptoms

A Spearman's correlation coefficient which assessed the relationship between childhood OCP traits and the duration of specific clinical symptoms (illness, amenorrhea, excessive exercise, fasting, laxative or diuretic use and vomiting) found no significant associations.

5.6.5 Analysis of OCP traits as heritable

Legend

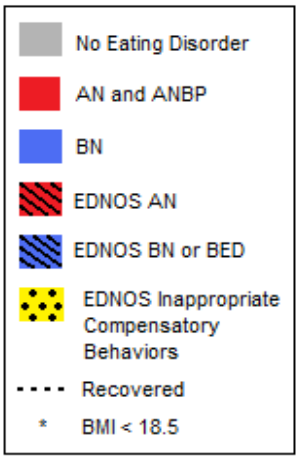
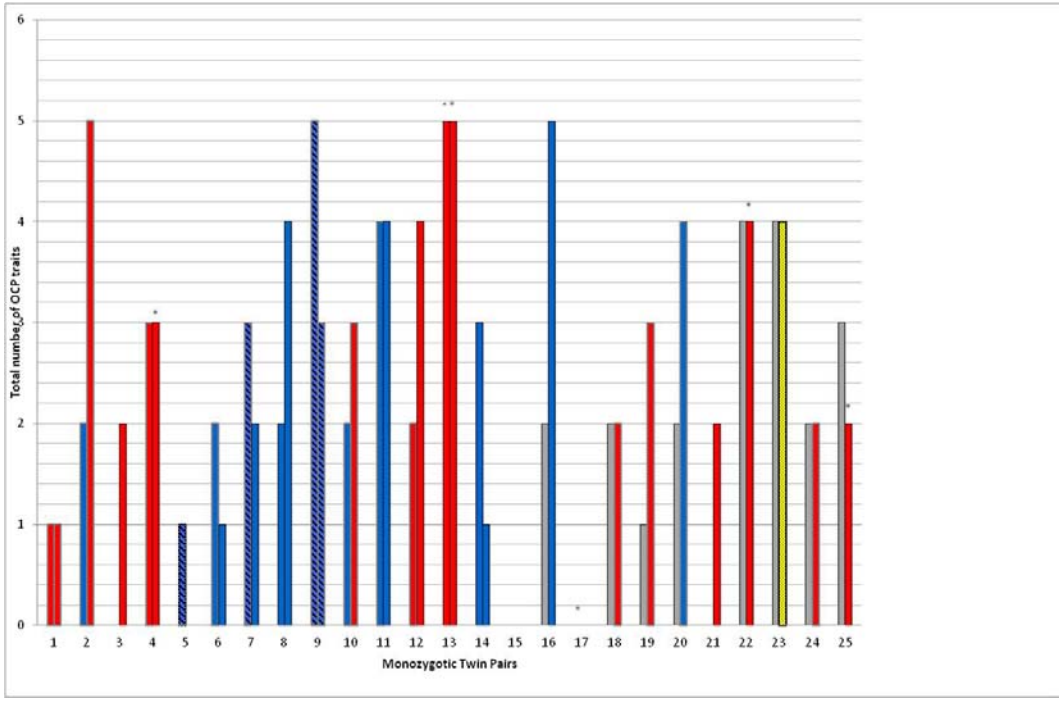


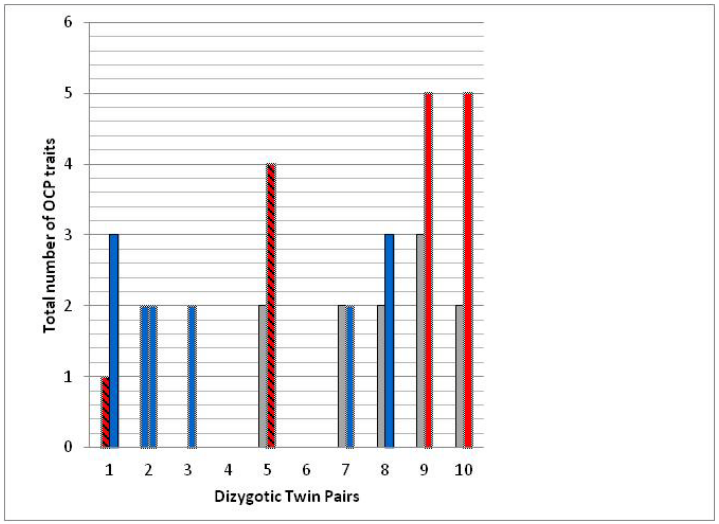
Diagram 5.1: OCP Traits in MZ and DZ Twins

Diagram 5.1a: OCP Traits in MZ Twin Pairs



Y axis: Total number of childhood obsessive compulsive personality traits
X axis: Twin pair (Twin pairs 1 to 14 are concordant for eating disorder diagnosis. Twin pairs 15 to 25 are discordant with twin 2 indicating the probands)

Diagram 5.1b: OCP Traits in DZ Twin Pairs



Y axis: Total number of childhood obsessive compulsive personality traits
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)

5.6.5.1. Summary of OCP traits as heritable

A visual inspection of diagrams 5.1a and 5.1b suggests within pair similarity in both MZ and DZ twins. The MZ within pair correlation [r=0.55 (CI: 0.21-0.77) p=0.00] was not higher than the DZ within pair correlation [r=0.74 (CI: 0.25-0.93) p=0.01] suggestive of a stronger influence of environmental factors.

5.7 Discussion

The aim of the present study was to investigate childhood personality traits reflecting OCP in EDs as familial and heritable traits. The traits were investigated using a semi-structured interview, requiring participants to give a retrospective account of OCP behaviour in childhood or prior to the onset of the ED. The findings confirmed that OCP traits were found at a higher rate in those with an ED history in comparison to controls and investigations into their unaffected twin siblings indicated that these were a strong familial liability. Lastly, investigations into heritability found a similar level of within pair similarity in MZ and DZ twins, suggesting that environmental factors shared by sibling pairs may contribute strongly to these traits.

5.7.1 Childhood OCP traits as a familial risk

All five OCP traits were more prevalent in the probands in comparison to controls. When comparing AN probands with BD probands, there was no overall statistical difference in the total number of childhood OCP traits (Anderluh et al 2003). This may in part be due to the limited sample size and lack of statistical power. A review of the descriptive statistics did however suggest a higher prevalence of some OCP traits in AN in comparison to BD probands. There were trends to suggest that those with AN were more likely to have reported excessive doubt and cautiousness and rule bound traits in childhood. Furthermore asides from two probands with BED (n=2), those with lifetime AN-R (76.9%) had the highest prevalence of perfectionism, in comparison to AN-BP types (54.4%) and BN (62.5%). This finding is supported by others (Anderluh et al 2003).

There was little evidence to support the prognostic significance of OCP traits in our sample. This is similar to previous investigations in a sample of 49 children and adolescents (aged 11-18) with AN, where no significant relationships between OCP traits and AN symptoms (restraint, eating concern, weight and shape) were found (Serpell et al 2006).

Four of the OCP traits (perfectionism, inflexibility, rule bound traits and excessive doubt and cautiousness) were familial traits since they were significantly elevated in their non-eating disorder cotwins. Specifically elevated levels of perfectionism in the unaffected twin siblings' supports previous research, which has found it to be a shared familial trait (Karwautz, et al 2001; Lilenfield, 2000). Premorbid inflexibility and rule bound traits were elevated in probands and the risk was 7.5-6.25 times higher in non-eating disorder cotwins in comparison to controls. Excessive doubt and cautiousness was found to be a familial trait, which is similar to previous findings of this in unaffected relatives of probands bulimia nervosa (Lilenfield et al, 2000). Although the need for order and symmetry was not significantly elevated in non-eating disorder cotwins the risk of this trait was 7.2 times more likely in this group in comparison to controls. Previous research has found the need for order, to be a familial trait, which is predictive of OCD symptoms such as washing and checking behaviours in daughters of mothers with OCD (Taberner et al 2009).

5.7.2 Childhood OCP traits as heritable

MZ twins did not demonstrate more frequent within pair similarity in comparison to DZ twins suggesting that environmental factors shared by sibling pairs may contribute strongly to these traits. Environmental precipitants that have been previously linked to OCP traits could include perinatal factors such as the maternal reporting of stress during pregnancy (Favaro and Santonastaso, 2010; Favaro and Santonastaso, 2008). As mentioned previously in chapter 4 (section 4.7.1), environmental factors could also include post natal factors such as feeding difficulties or adversities in childhood which are markers of the future development of eating disorders (Micali 2005). Anecdotal evidence gathered from the semi-structured interview also suggests that strict parenting and school styles may have contributed to excessive doubt and cautiousness and rule bound traits.

Previous research which has investigated the exact contributions of genetic and environmental influences to childhood OCP traits (measured by the childhood retrospective perfectionism questionnaire; Southgate et al 2008) in a large sample of representative twins (TwinsUK dataset) has found genetics to account for 0.81 of the variance and non-shared environmental factors to account for the remaining 0.19 (Boraska et al, to be submitted). Other studies of representative samples have found a wide range in the heritability OCPD (defined by the DSM-IV and DSM-III-R) ranging from 27 to 77% (Reichborn Kjennerud et al 2007; Torgersen et al 2000). Various factors could explain these very differential genetic factors of OCP traits between our clinical sample and the representative sample. Firstly, the limited sample size of our clinical twins and the possibility that this leads to false positives is noted. Secondly, the underlying phenotypes or rather, the etiological architecture of OCP features may differ between clinical and control populations. This idea is elaborated by Gottesman and Gould (2003) who proposed that the genetic correlation between clinical symptoms and the underlying phenotype differs between psychiatric and healthy populations. To confirm these proposals, further research with much larger samples of twins with clinical eating disorders are required to accurately conduct heritability estimates of OCP features.

5.7.3 Limitations of the study

The present study lends support to the importance of environmental factors in the development of OCP traits. However this suggestion cannot be formally confirmed due to the aforementioned limitation of not having systematically assessed pre and postnatal environmental events (see chapter 4, section 4.7.1).

Other limitations include the use of a twin sample. It may be queried as to whether this sample is representative of the singleton population of eating disorders. Extreme competitiveness between siblings, may contribute to perfectionistic tendencies and this may be especially the case for identical twins. Competing for superiority in terms of physical appearance, parental affection or academic achievements was something that was reported by the twins during the

semi-structured interview. Empirical investigation into the influence of competitiveness between siblings on the heritability of specific traits deemed it to be a negligible factor (Rebollo and Boomsma 2006).

Positive features of this study are the use of a semi-structured interview to assess childhood OCP traits which probed participants to recall a range of behavioural examples. In comparison to self-report measures, this method possibly allowed for a more representative account of their true behaviours and attitudes. Furthermore, the present study assessed these behaviours as risk factors that were not confounded by the presence of an ED, since participants reported OCP behaviour prior to the ED onset.

Previous neuropsychological assessments of inflexibility have also found cognitive inflexibility to be a familial trait (Holliday et al 2005; Roberts et al. 2010). However it has been suggested that neuropsychological tasks such as the WCST (Heaton et al 1993), measure more general executive functioning and cognitive inflexibility as opposed to behavioural flexibility (Kremen et al (2007). A study which did not find significantly more errors on the WCST (Heaton et al 1993) in adolescents with AN, did find significantly more difficulties in cognitive and behavioural set shifting measured by a self report measure (Behavior Rating Inventory of Executive Function-Self Report) (McNarney et al 2011). By assessing behavioural inflexibility using a semi-structured interview, the present study addresses this limitation.

5.8. Conclusion

To summarise, all five childhood OCP traits were found to be significantly elevated in probands. Furthermore these OCP traits, apart from the drive for order and symmetry were found to be significantly elevated in their non-ED cotwins. This suggests that they are shared familial risks that are the product of shared environment and genes. MZ twin pairs did not demonstrate greater within pair similarity in comparison to DZ twins suggesting that shared environmental factors of the twin siblings contribute substantially to these OCP traits. It may be proposed that future studies should aim to assess OCP in terms of its five distinct components as opposed to the over-arching diagnostic category. This may assist in refining the phenotype by enabling more accurate investigations into the aetiology of OCP traits in EDs.

6. Chapter 6: Impulsive Behaviours in Women with Eating disorders: An Investigation in Twins

6.1 Introduction to the chapter

The previous chapter investigated the OCP traits known to characterise all eating disorder types. Following on from this, the present chapter investigates impulsive behaviours that more typically define eating disorders with a binge eating component.

These behaviours are investigated in terms of their endophenotype criteria which include a familial and heritable risk as outlined by Gottesman and Gould (2003). Support for this hypothesis merits the exploration of related behavioural traits such as an altered sensitivity to reward as potential endophenotypes and possible additions to the diagnostic assessment in Chapter 9.

6.2 Background and development of the study

As mentioned in the introduction (section 1.15), impulsive behaviours consistently characterise eating disorders – in particular, those marked by binge eating in comparison to restrictive types (Favarro et al 2005; Fernandez-Aranda et al 2008). These behaviours are predictive of long term outcome and response to treatment indicating that they have potential use in the diagnostic process and clinical settings (Fichter et al 2006; Fahy and Eisler, 1993; Fernandez-Aranda et al 2008, Fernandez-Aranda et al 2006).

Evidence from research in twins and sibling pairs indicates that these traits are familial and genetic risk factors (Wade et al 2008; Karwautz et al 2002; Wade et al 2004; Congdon and Canli, 2008; Hur and Bouchard, 1997; Pedersen, Plomin, McClearn & Friberg, 1998). The focus of the present study was to investigate the familial and genetic risk of lifetime impulsive behaviours measured by the EATATE lifetime diagnostic interview (Anderluh et al 2003) in twins with eating disorders.

6.3 Aims

The aim of this study was to explore whether lifetime impulsive behaviours measured by the EATATE diagnostic interview (Anderluh et al 2003) might be considered as endophenotypes using a genetically sensitive design (a twin study). Three endophenotype criteria outlined by Gottesman & Gould (2003) were investigated: a) lifetime impulsive behaviours are associated with EDs, b) co-segregation within families and c) heritability.

6.4 Hypotheses

The main hypothesis was that impulsive behaviours would be more characteristic of those with a lifetime diagnosis of BD in comparison to those with AN. Moreover investigations into their twin siblings would indicate that these are familial and genetic risks factors.

6.4.1 Specific objectives and predictions:

According to the current evidence base the following predictions were made:

Firstly, the association between lifetime impulsive behaviours and the illness was examined by comparing ED twins with controls. It was hypothesised that BD probands would have elevated levels of lifetime impulsive behaviours in comparison to controls and AN probands.

Secondly, to assess co-segregation within families, the presence of these traits in non-eating disorder cotwins were examined. It was hypothesised that non-eating disorder cotwins would show similar levels of lifetime impulsive behaviours to their probands. Therefore non-bulimic disorder cotwins would have elevated levels of lifetime impulsive behaviours in comparison to controls and non-AN cotwins.

Thirdly, impulsive behaviours were assessed in relation to other clinical features of the disorder in probands. It was expected that a higher number of impulsive behaviours would be associated with greater clinical severity.

Lastly, heritability was examined by comparing MZ and DZ twins with the expectation that lifetime impulsive behaviours would be more similar within MZ twin pairs in comparison to DZ twin pairs.

6.5 Methods

6.5.1 Study design

This study employed a cross sectional case-control study design to compare clinical and control groups. A familial design (chapter 3, section 3.15.5) was employed to assess non-ED cotwins in comparison to controls and a twin design (chapter 3, section 3.15.6) was employed to assess the genetic risk of lifetime impulsive behaviours.

6.5.2 Participants

Participants were the clinical and control group described in chapter 5 (table 5.1).

6.5.3 Measures

The measures used in this study were the same as used in chapter 4 (and described in detail in chapter 3, sections 3.5.3 and 3.5.4).

6.5.4 Data analysis

In the present study normality of the data was assessed separately for each comparison between the groups. Transforming the data did not reduce the skew, therefore the non-parametric method of the Mann-Whitney U test was used to assess comparisons between groups.

6.5.5. Sample size and power

The post hoc power analysis indicated that the present sample would have 100% and 100%, power for detecting group differences between AN probands and BD probands and controls at the 0.05 level for lifetime impulsive behaviours (based on Anderluh et al 2003).

6.6 Results

6.6.1 Demographic features of clinical twins and controls

Demographic and clinical details of the clinical and control groups are presented in chapter 5 (table 5.1).

6.6.2 Analysis of lifetime impulsive behaviours as associated with eating disorders and as a familial trait

Table 6.1: Impulsive Behaviours in Probands, Non-Eating Disorder Cotwins and Control Singletons

Lifetime impulsive behaviours								
	AN Proband (n=24)	***Non-AN cotwin (n=12)***	***BD Proband (n=26)***	***Non-BD cotwin (n=6)***	***Control singleton (n=28)***			
Total number of lifetime impulsive behaviours (NB)	1 (1.5)	1.5 (1)	3 (2.5)	3 (2.5)	0 (0)	***EDs vs. Controls***	***Test Statistic***	***Cohen's d***
						AN vs. controls	*U*=103.5, p=0.00	(d=1.81)
						BN vs. controls	*U*=22.5, p=0.00	(d=3.25)
						Non-AN cotwin vs. controls	*U*=22.5, p=0.00	(d=2.64)
						Non-BN cotwin vs. controls	*U*=1.5, p=0.00	(d=2.92)

AN: anorexia nervosa probands
BD: bulimic disorder probands (bulimia nervosa and binge eating disorder)
Non-AN cotwin: Non anorexia nervosa cotwins
Non-BD cotwin: Non bulimic disorder (bulimia nervosa and binge eating disorder) cotwins
NB: This analysis excludes the twin pair whose proband had EDNOS inappropriate compensatory behaviours
Total number of lifetime impulsive behaviours: 12 impulsive behaviours (excluding binge eating) measured by the EATATE part II interview
Statistics reported are medians, followed by interquartile ranges (IQ) in brackets for the total number of lifetime impulsive behaviours.
Test Statistic: Mann Whitney U Test and Cohen's d effect sizes presented

6.6.3 Lifetime impulsive behaviours as predictors of eating disorder symptoms

The total number of impulsive behaviours (i.e. alcohol or substance abuse, stealing, gambling, hitting, provoking fights, self-harm, overdosing, overspending, fire setting, disinhibited sexual activity, excluding bingeing) was significantly associated with the duration of bingeing (r=0.41, p=0.01) and vomiting (r=0.32, p=0.00) with a moderate sized correlation coefficient. Assessing these associations using a linear regression analysis with age as an additional covariate indicated that lifetime impulsive behaviours was not a significant predictor of bingeing. However the number of impulsive behaviours was found to account for 23.9% of the variation in vomiting. Therefore every additional impulsive behaviour reported increased the duration of vomiting by 19.4 months. These interpretations are only held true if the effects of age are held constant.

6.6.4 Analysis of impulsive behaviours as heritable

Legend

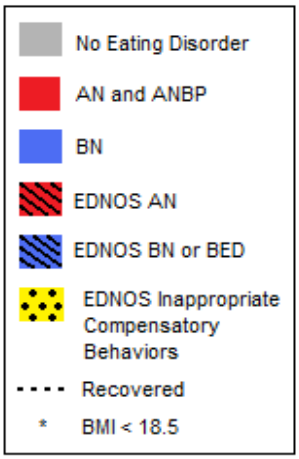
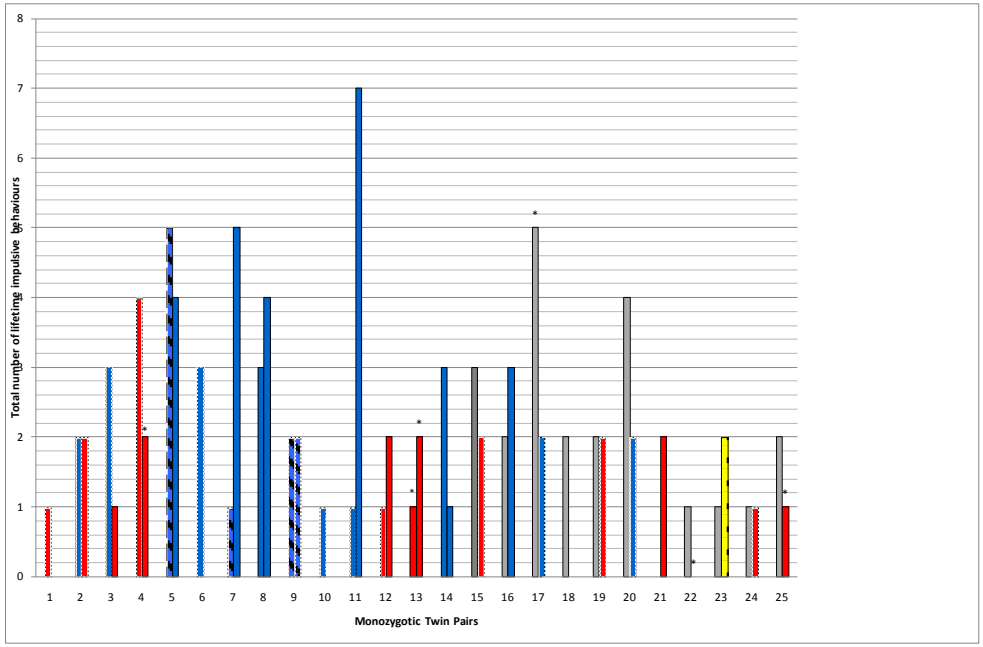


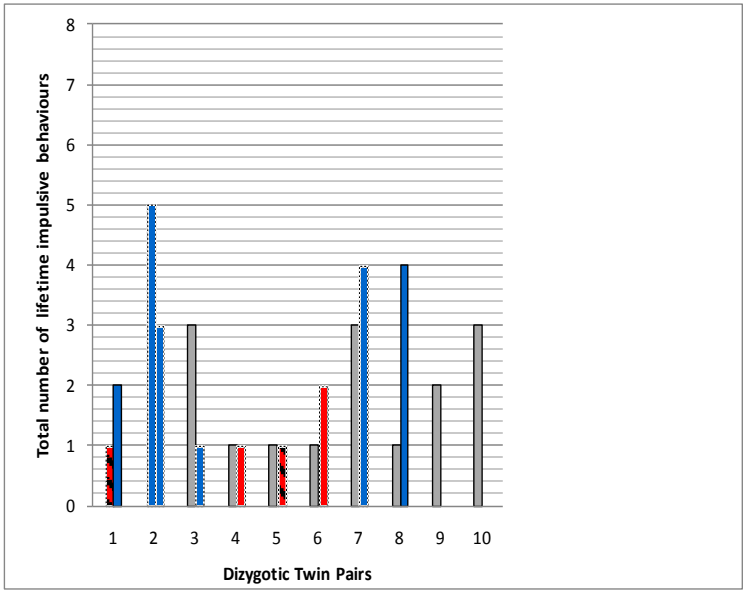
Diagram 6.1: Lifetime Impulsive Behaviours in MZ and DZ Twins

Diagram 6.1a: Lifetime Impulsive Behaviours in MZ Twin Pairs



Y axis: Total number of lifetime impulsive behaviours
X axis: Twin pair (Twin pairs 1 to 14 are concordant for eating disorder diagnosis. Twin pairs 15 to 25 are discordant with twin 2 indicating the proband)

Diagram 6.1b: Lifetime Impulsive Behaviours in DZ Twin Pairs



Y axis: Total number of lifetime impulsive behaviours
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)

6.6.4.1 Summary of lifetime impulsive behaviours as heritable

A visual inspection of diagrams 6.1a and 6.1b suggests limited within pair similarity in both MZ and DZ twins. The MZ within pair correlation [r=0.06 (CI: -0.34-0.44) p=0.30] was not higher than the DZ within pair correlation [r=0.12 (CI: -0.52-0.67) p=0.39].

6.7 Discussion

The aim of the present study was to investigate lifetime impulsive behaviours in eating disorders as familial and heritable traits. The traits were investigated using a semi-structured interview, requiring participants to give an account of the impulsive behaviours that they had engaged in and had felt significant feelings of lack of control. The findings confirmed that bulimic disorders had engaged in more lifetime impulsive behaviours than controls and anorexic probands. Furthermore, the propensity for impulsive behaviours was also found to be a shared familial liability.

6.7.1 Impulsive behaviours as predictors of eating disorders

Lifetime impulsive behaviours were significantly associated with the duration of bingeing, however a regression analysis found that it was not a significant predictor of this symptom. This may be due to the difficulty in clarifying feelings of lack of control whilst bingeing (Bulik et al 2008). There was also the difficulty in distinguishing between an objective binge, which is defined by the DSM-IV (APA, 2000) as consuming over 1000 calories and a subjective binge which may often occur in binge purge types who retain an underweight status (i.e. ANBP). The more distinct impulsive eating behaviour of vomiting was significantly predicted by the number of lifetime impulsive behaviours. It may be that impulsive eating behaviours and general impulsive behaviours are used as a substitute for one another over the life course due to difficulties in self regulation or as a maladaptive emotional regulation strategy (Marsh et al 2009; Uher et al 2004; Heatherton and Baumeister, 1991). Furthermore impulsive eating behaviours may have a synergistic effect, which increases the use of general impulsive behaviours over time. Animal models support this and demonstrate that periods of fasting and purging contribute to addictive behaviour (Rada et al 2005; Avena et al 2005; Boggiano et al 2007; Boggiano et al 2005; Avena & Hoebel 2003; Corwin 2006; Corwin & Hajnal 2005).

6.7.2 Impulsivity as familial

Impulsive behaviours were found to be elevated in all EDs although most prevalent in those marked by binge eating in comparison to restrictive types, which is line with previous findings (Favarro et al 2005; Fernandez-Aranda et al 2008). Interestingly similar patterns were found in their non-ED cotwins with a higher number of impulsive behaviours in non-BD cotwins in comparison to non-AN cotwins. Other research has demonstrated an elevated prevalence of alcohol and substance use disorders in family members of women with bulimia nervosa and an increased ‘sensitivity to reward’ in unaffected siblings of those with EDs (Bulik, 1991; Kaye et al 1996; Karwautz et al 2002).

6.7.3 Impulsivity as heritable

There was less evidence to support a substantial genetic basis for the number of lifetime impulsive behaviours. Since this behaviour was found to be a familial risk as opposed to

genetic, it may indicate that it is more susceptible to shared environmental factors that encourage behaviours involving lack of control and addiction. These may include certain eating behaviours that encourage the use of general impulsive behaviours over time (Rada et al 2005; Avena et al 2005; Boggiano et al 2007; Boggiano et al 2005; Avena & Hoebel 2003; Corwin 2006; Corwin & Hajnal 2005) or pre and postnatal factors that cause the epigenetic modification of genes and possibly the propensity for impulsive behaviours (Barker and Osmond, 1986; Micali 2005).

6.8 Conclusion

To summarise lifetime impulsive behaviours were found to be characteristic of bulimic eating disorders and their unaffected co-twins, suggesting that it is a shared familial liability. Less evidence was found to support a strong genetic basis of these traits since large discordances were found within many MZ twin pairs. On the basis of there being a synergistic relationship between impulsive behaviours and the duration of vomiting and bingeing, it was suggested that certain eating behaviours may encourage changes in brain biology which increase the risk of impulsive behaviours over time.

7. Chapter 7: Set shifting and Central Coherence as Neurocognitive Endophenotypes in Eating Disorders: A Preliminary Investigation in Twins

7.1 Introduction to the chapter

This chapter describes the fifth experimental study of this thesis, which explores the genetic basis of set shifting and central coherence in twins with eating disorders. Previous research has shown that weak central coherence and poor set shifting are risk markers for eating disorders, that are present post recovery (Tchanturia et al, 2011; Teconi et al, 2010; Nakazato et al, 2010; Nakazato et al, 2008; Tchanturia, et al, 2004) and in first degree relatives (Roberts et al. 2010; Holliday et al. 2005; Tenconi et al. 2010). The aim of this study was to examine these traits in twins with eating disorders to explore the familial and genetic risk using endophenotype criteria as outlined by Gottesman and Gould (2003).

7.2 Background and development of the study

A variety of neurocognitive traits are being investigated as possible additions to diagnostic assessments. As mentioned in the introduction (Chapter 1, section 1.16) the eating disorder neurocognitive profile includes inefficiencies in set shifting and weak central coherence (Roberts et al. 2007; Lopez et al. 2008d). It is possible that inefficiencies in set shifting (Tchanturia et al. 2011; Teconi et al. 2010; Nakazato et al. 2010; Nakazato et al. 2008; Tchanturia, et al. 2004) and weak central coherence (Harrison, Tchanturia and Treasure, 2011; Teconi et al. 2010; Lopez et al. 2008b) represent vulnerability traits as they remain in those recovered and are present in non-eating disorder sisters suggesting that they are familial traits (Roberts et al. 2010; Holliday et al. 2005; Tenconi et al. 2010; Roberts, Tchanturia and Treasure, submitted). However the design of these studies does not distinguish between the effects of shared environment or genes. To parse out the exclusive effects of genetic factors, differences within identical twin pairs would need to be investigated. This will form the focus of the present chapter.

7. 3 Aims

The aim of this study was to explore whether set shifting and weak central coherence might be considered as endophenotypes using a genetically sensitive design (a twin study). Three endophenotype criteria outlined by Gottesman & Gould (2003) were investigated: a) the association of difficulties in set shifting and weak central coherence with EDs, b) co-segregation within families and c) heritability.

7.4 Hypotheses

The main hypothesis was that people with eating disorders would have inefficiencies in set shifting and weak central coherence and investigations into their twin siblings would indicate that these are familial and genetic risks factors.

7.4.1 Specific objectives and predictions for set-shifting

Firstly, to assess whether this study would replicate previous findings, the association between set-shifting and the illness was examined by comparing eating disorder probands with controls. It was expected that probands would have inefficiencies in set shifting in comparison to controls.

Secondly, to assess co-segregation within families, set-shifting in non-eating disorder cotwins were examined. It was expected that non-eating disorder cotwins would also have inefficiencies in set shifting in comparison to controls.

Thirdly, set-shifting was assessed in relation to clinical features of the disorder in probands. It was expected that greater inefficiencies in set-shifting would be positively associated with clinical severity.

Lastly, the heritability of set-shifting was examined by comparing within pair similarity for MZ and DZ twins. Since previous research has demonstrated set-shifting to be a familial trait (Tenconi et al 2010; Robert et al 2010) it was expected that set-shifting performance would be heritable. Therefore set-shifting performance within monozygotic twin pairs would be more similar in comparison to dizygotic twin pairs.

7.4.2. Specific objectives and predictions for central coherence

Firstly, the association between central coherence and the illness was examined by comparing eating disorder twins with controls. It was expected that probands would have weak central coherence in comparison to controls.

Secondly, it was expected that AN probands would have weaker central coherence in comparison to BD probands.

Thirdly, to assess co-segregation within families, the presence of these traits in non-eating disorder cotwins were examined. It was expected that non-eating disorder cotwins would also have weak central coherence in comparison to controls.

Fourthly, central coherence was assessed in relation to clinical features of the disorder in probands with the expectation that weaker central coherence would be associated with greater clinical severity.

Lastly, the heritability of central coherence was examined by comparing within pair similarity for MZ and DZ twins. Since previous research (Roberts et al, submitted; Tenconi et al 201) has indicated central coherence to be a familial trait it was expected that central coherence would be heritable. Therefore central coherence within monozygotic twin pairs would be more similar in MZ twins in comparison to DZ twin pairs.

7.5 Method

7.5.1 Study design

This study employed a cross sectional case-control study design to compare clinical and control groups. As described in chapter 3, a familial design (section 3.15.5) was employed to examine the familial risk of these traits by comparing non-eating disorder cotwins with controls and lastly a twin design (section 3.15.6) was employed to assess the genetic risk of these neurocognitive traits.

7.5.2 Participants

The participants used in this study are those described in chapter 3 (3.10). The clinical group included twins where at least one twin met DSM-IV criteria for an eating disorder and control twins. Specifically the clinical group included a total of 72 twins from 26 monozygotic and 10 dizygotic twin pairs. The control group included a total of 42 twins. Recruitment procedures for the clinical and control groups are described in detail in chapter 3 (section 3.3.1).

7.5.3 Materials:

7.5.4 Clinical assessment

The EATATE semi-structured interview (sections 3.5.3 and 3.5.4) was administered to all probands and non-eating disorder cotwins (Anderluh et al 2003). All participants also completed the NART (Nelson and Wilson 1991; section 3.4.3) as an indication of premorbid IQ, the OCI-R (Foa et al 1998; section 3.6.2) to assess obsessive compulsive symptoms, the DASS (Lovibond and Lovibond, 1995; section 3.6.1) to assess depression and anxiety and the Rosenberg self-esteem measure (Rosenberg, 1984; section 3.6.3). The aforementioned measures are described in greater detail in chapter 3.

7.5.5 Neuropsychological assessment

7.5.6 Measures of set shifting

All participants were administered the neuropsychological battery which consisted of several paradigms assessing both set shifting and central coherence. These are described below.

7.5.6.1 Wisconsin card sort task (WCST) (original manual version by Grant and Berg, 1984; computerised version by Heaton, Chelune, Talley, Kay, and Curtiss, 1993)

The WCST is a measure of cognitive flexibility. In the present thesis the computerised version was used. To begin participants are presented with a screen, which displays four cards in a row. These include cards with 1 red triangle, 2 green stars, 3 yellow crosses and 4 blue circles. Underneath there are 4 blank boxes in a row. At the bottom of the screen there is a pile of cards faced upwards. Participants are given the instruction that the four cards at the top will stay the same throughout the task. They are told that they are required to match each card from the pile at the bottom with the row of cards displayed at the top according to which they think fits best. The cards may be sorted according to 1 of 3 rules which include matching its 'shape', 'number' or 'colour'. To do this participants are told to click on the blank box below the card and the computer will move the card for them. The time taken for the card to move is 1.5 seconds, during which the participant can change their mind by clicking anywhere on the screen, enabling them to retry. However once the card has moved to the box the choice cannot be changed. The participant is told that once the card has moved to the pile they will receive visual and audio feedback informing them of whether they have sorted the card correctly. Visual feedback is given in the form of 'Right' or 'Wrong' being flashed on the screen for 1 second. The audio feedback reads out of the visual feedback. They are told that they may use this feedback to determine how they sort the next card. Throughout the task the sorting rule changes unpredictably requiring the participant to adapt to new rules or stay with the same. After every 10 cards that are sorted correctly the rule changes in the following order: colour, shape, number, colour, shape, number and so on. To begin the card must be sorted according to the rule of colour. The task comes to an end, when the participant has correctly sorted all the cards for 6 consecutive rules, or when all 128 cards have been sorted. The task can be completed with sorting a minimum 70 number cards. Participants are told that there is no time limit. No further instructions are given.

The WCST measures a wide range of executive functions relating to the frontal lobe, such as working memory, reward and inhibition. In the present study, this task was used to measure set-shifting ability, with greater difficulties being determined by a higher number of perseverative errors. When the participant sorts the card according to a previous rule that is no longer correct, a perseverative error has occurred.

The WCST provides a number of output variables, which include the raw number of perseverative errors in addition to the percentage of perseverative errors. In this study the raw score was used in the analysis since a percentage can be misleading. For example a participant needing more cards to complete the task than another who scored the same number of perseverative errors will result in a lower percentage of perseverative errors than the former. In such cases the contribution of perseverative errors to the overall percentage is decreased. Therefore the raw number of perseverative errors is chosen as the most sensitive measure of set shifting ability.

7.5.6.2 Brixton task (Burgess and Shallice, 1997)

The Brixton task is a cognitive set-shifting task (see appendix 1.11). Originally administered using a paper version and as part of the Brixton & Hayling task set. This thesis used a computerised version. Participants were presented with a computer screen on which there is a grid 5 x 2 grid of white circles. The circles on the top row are labelled 1 to 5 and the circles on the bottom row are labelled 6 to 10. At the beginning of the task, circle 1 is blue. Participants are told that the blue circle will move location and that they are requested to predict the next movement of the blue circle by saying their prediction out loud. After each prediction is made, the experimenter prompts the blue circle's next move using the computers keypad. Participants were told that the blue circle may move in a sequence and that this pattern of movement will change throughout the task requiring them to adapt to the new pattern to avoid making errors. In total the blue circle moves 55 times with the blue circle's pattern of movement changing 8 times. The blue circles first movement of each new pattern is scored as correct if the participant has responded in accordance with the old rule. Subsequent trials are only scored as correct if the participant has by then adapted to the new rule. The experimenter records the participants' responses on a sheet allowing them to total the outcome variable, which is the total number of errors. A higher number of errors are indicative of greater difficulties in set-shifting.

7.5.6.3. Justification of set shifting measures selection

Two measures of set shifting were chosen based on previous research. In Roberts et al (2007) systematic review of set shifting in eating disorders, the Wisconsin Card Sorting Task (WCST) yielded a medium effect size (d=0.62) when comparing AN with controls. This indicates that it is a sensitive measure for AN. Furthermore, recently a study using discordant sisters has shown that non-AN sisters had more perseverative errors on the WCST with a medium effect size suggesting that it is a sensitive measure of familial risk (Roberts et al 2010). The WCST (described in detail in section 7.5.6.1) is relatively costly, however being a computerised task it offers an objective measure. Furthermore with it being one of the most widely used measures of set shifting, the present findings can be interpreted within a wide context of twin research in other psychiatric and control samples. The WCST is argued to measure a wide variety of executive functions, one of which is set shifting, meaning that poor performance on this task could be indicative of many underlying deficits (Kremen et al 2007). Therefore another measure

of set shifting ability was included; the Brixton task. The systematic review conducted by Roberts et al (2007) yielded a small effect size of 0.21 when comparing those with AN and BN to controls. Importantly the Brixton task and the WCST differ in levels of complexity. In the WCST task, participants are not given explicit instructions that they will need to adapt to new rules throughout the task, although this is the case in the Brixton task. Furthermore in the WCST, participants are told whether their response is correct, allowing them to learn from feedback (Tchanturia et al 2012).

The Brixton task has also demonstrated its sensitivity in detecting a familial risk in non-BN sisters since a medium effect size was found in comparison to controls (Roberts et al 2010). The Brixton task (described in detail in section 7.5.6.2) can be administered relatively quickly (approximately 3 minutes) and can be purchased cheaply. Including this task would enable the findings of the present study to be compared within the context of other research, which has assessed the familial risk of deficits in eating disorders (Roberts et al 2010).

7.5.7 Measures of central coherence

7.5.7.1. Group embedded figures task (GEFT) (Witkin, Oltman, Raskin, & Karp, 2002)

The GEFT is an assessment of local processing. It assesses the time taken to locate a simple geometric figure within a meaningless geometric pattern (see appendix 1.12). The task, which is administered individually, is presented in a booklet, which is split into 3 sections each containing 9 trials. The 1st section is a practice. The study adopts a modified version used by Booth (2006), which simultaneously presents the trial and the simple shape to the participant. Therefore, performance on this task is not confounded with working memory abilities. The participant is told that the simple shape will be depicted within the complex shape in the same shape, size and orientation. For the procedure the participant is first shown the simple shape, with the complex shape being revealed soon after. At this point the stopwatch is started. When the participant indicates that they have found the shape, the stopwatch is paused. The participant then traces in the shape. If the participant's guess is incorrect, a 'false claim' is recorded and the stopwatch is restarted. Each trial comes to an end when the participant successfully locates the simple shape, or after the maximum time of 60 seconds, which is recorded as a 'time-out error'. Since the booklet is double-sided, other complex shapes that are not relevant to the current trial are hidden using another piece of paper. The time taken to locate all 18 shapes, in addition to the number of false claims and time out errors are recorded. A shorter response time indicates superior local processing.

The GEFT is based on work by Gosttschaldt (1926) who originally developed a measure of Gestalt perception, which involved locating shapes that were embedded within line patterns. Witkin (1971) developed this further with the embedded figures task (EFT), by presenting the complex figure in various colours and making the simple shape harder to locate. The EFT was

originally developed with the possibility of being administered in group settings (Witkin 1971). Subsequently the GEFT which is based on the EFT was developed. This task included figures from Gosttschaldts work and the EFT. In this task the complex design is presented in shades of blue as opposed to various colours. The GEFT has been validated as a reliable measure of detail processing in a student sample (Witkin 2002).

7.5.7.2 Rey-osterrieth complex figure (ROCF) task (Osterrieth, 1977)

This task is an assessment of global integration and detail focus. The participant is required to copy a complex figure which assesses their organisational strategy. The participant is provided with a blank sheet of paper and another paper depicting the ROCF figure (Diagram 7.1). They are also provided with 10 colour pencils in the following order; black, green, purple, brown, blue, pink, light blue, red, orange and yellow. The participant is asked to copy the figure starting with the black pencil first. During the process, the experimenter prompts the participant to change their pencil by handing them the next pencil. To assist the scoring procedure the drawing is filmed.

7.5.7.2.1 Central coherence index

The drawing is scored according to the system developed by Booth and colleagues (2006), which results in a central coherence index. This score ranges from 0 to 2 and higher scores indicates less detail (local) focus and the use of more global strategies. The index is derived by taking into account the order and style of the drawing.

7.5.7.2.2. Central coherence order

Central coherence order is a score which quantifies whether the drawing was constructed by starting with its more detailed elements as opposed to its more global or exterior elements. The 18 elements are classed into one of 4 categories; 1) global external element, 2) global internal element, 3) local perimeter element and 4) local internal element (see table 7.1). The score is based on the mean of the first 6 elements drawn resulting in a score of 0 to 3.2. This score is then divided by 3.2 to give a weighted central coherence order index, ranging from 0 to 1.

7.5.7.2.3 Central coherence style

Central coherence style is a score which quantifies whether the 6 key elements were drawn in a continuous or fragmented manner. These elements include the large rectangle (element 2), the diagonal cross (element 3), the extended horizontal line (elements 4 & 16), the extended vertical line (element 5), the sides of the large triangle (element 13), and the small rectangle (element 6) (see figure 1). Each element is given a score ranging from 0 to 2. A score of 0 indicates that the element was drawn in a fragmented manner with at least 2 interruptions. Key elements, which are not drawn, are also given a score of 0. A score of 2 indicates that the element was partially fragmented and interrupted once. A score of 2 indicates that the element was drawn in a continuous manner with no interruptions. The mean score of the 6 elements

gives a score of 0 to 2, which is then divided by 2 to give a weighted central coherence style index ranging from 0 to 1.

The weighted central coherence style and order indices are added together to give the central coherence index ranging between 0 to 2, with higher scores indicating better global integration and lower scores indicating more detail focus.

Diagram 7.1: Elements of the ROCF Task

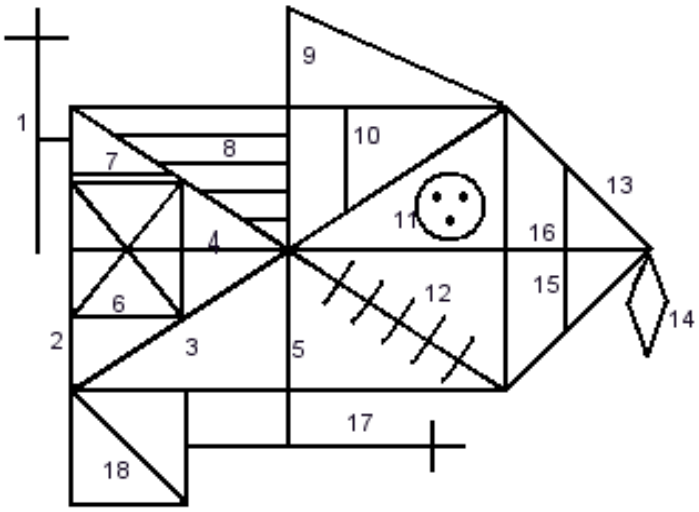


Table 7.1: ROCF Hierarchical Categories for the Order of Construction

Category	**Element**	**Description**
Global external element (Score = 4)	2	Large Rectangle
	13	Sides of the large triangle attached to large rectangle
Global internal element (Score= 3)	3	Diagonal cross
	4	Horizontal middling of large rectangle
	5	Vertical midline of large rectangle
	6	Horizontal line within sides of large triangle
Local perimeter element (Score=1)	1	Vertical cross
	9	Small triangle above large rectangle
	14	Diamond
	17	Horizontal cross
	18	Square attached to large rectangle
Local internal element (Score=0)	6	Small rectangle
	7	Small horizontal line above small rectangle
	15	Vertical line within sides of large triangle
	8	Four parallel lines
	10	Small vertical line within large rectangle
	11	Circle with three dots
	12	Five parallel lines

(Booth, 2006)

7.5.8. Justification of central coherence measures selection

The GEFT (Witkin, Oltman, Raskin, & Karp, 2002) was chosen as a measure of local processing. Lopez and colleagues' (2008d) systematic review indicated that the highest effect sizes for comparisons between controls and people with eating disorders were found for the version where participants are presented with the simple and complex design at the same time. In this version a detailed focused cognitive ability is not confounded with working memory. This version has found superior performance in EDs with a moderate effect size in comparison to the others, which have only found a difference with a small effect size (Lopez et al 2008a; Lopez et al 2008c). Furthermore this task has been previously trialled in a study of discordant sisters, which has demonstrated that this is a sensitive measure to assess this trait as a familial risk (Roberts et al submitted).

In addition the ROCF task (Osterrieth 1944) was chosen to assess both global integration and detail focus. Taking into account the systematic review conducted by Lopez et al (2008d) and subsequent studies (Roberts submitted; Harrison 2011), those with EDs differ from controls with the largest effect sizes on organisational strategy (central coherence index) in comparison to copy and recall accuracy outcome variables. Similarly non-ED sisters differ most from controls on organisational strategy (CCI) suggesting that this is the most sensitive measure to assess a familial trait (Roberts et al submitted). Therefore the copy accuracy and recall accuracy aspects of the tasks were not included.

7.5.9 Procedure:

Full details of the procedure are described in Chapter 3. Tasks were administered in the following order: WSCT, ROCF task, GEFT and the Brixton Test.

7.5.10 Statistical methods

The statistical procedures are those described in chapter 3.

For the analysis using a familial design (section 3.15.5) that compared, probands, non-eating disorder cotwins and controls, the data was transformed for outcome variables that were not normally distributed. A logarithm transformation was used for the WCST (perseverative errors), the Brixton test (total number of errors) and the GEFT (median time taken) outcome variables.

7.5.11 Sample size and power

The sample size in the present study was limited by the number of twins it was possible to recruit within a time frame. Due to the exploratory nature of this study a post-hoc power analysis was conducted using GPower software. This indicated that in order to detect group differences between probands and controls at the 0.05 significance level, the present sample would have 99% power for the WCST, 70% for the Brixton task, 97% for the ROCF and finally 51% power for the GEFT (based on Tchanturia et al 2012, Tchanturia et al. 2011; Roberts, Tchanturia and

Treasure, 2010; Roberts, Tchanturia and Treasure, submitted). For detecting group differences between non-eating disorder cotwins and controls at the 0.05 significance level the present sample would have 44% power for the WCST, 22% for the Brixton task, 99% power for the ROCF and 15% for the GEFT (based on Roberts et al. 2010; Roberts, Tchanturia, Treasure, submitted).

7.6 Results

7.6.1 Analysis of neurocognitive traits as associated with eating disorders and as familial traits.

7.6.1.1. Set-shifting

Table 7.2 represents the results from the set shifting tasks (WCST and the Brixton Task).

i) Eating disorder twins vs. control twins

Eating disorder probands had a significantly higher number of perseverative errors on the WCST in comparison to controls with a medium effect size (d=0.5, p=0.01) (see table 7.2). AN probands (d=0.6, p=0.04) had a slightly greater impairment in comparison to controls than BD probands (d=0.4, p=0.03). A descriptive comparison showed that those who were currently underweight (n=7, raw mean=18.23, s.d=10.91) had a higher number of perseverative errors than those who were weight recovered (n=46, raw mean =14.34, s.d =11.61) with a small effect size (d=0.3). For the analysis of the WCST perseverative errors, exclusion of two outliers from the proband group and one outlier in the control group did not largely change the effect sizes of group comparisons.

For set shifting measured by the Brixton task, probands had a higher number of errors in comparison to controls with a small effect size (d= 0.2, p=0.35) at trend level (see table 7.2). This impairment was slightly more pronounced in BD probands (d=0.3, p=0.18) than in AN probands (d=0.1, p=0.77) in comparison to controls. Those who were currently underweight (n=7, raw mean=11.00, s.d=3.32) had a lower number of errors than those who were weight recovered (n=46, raw mean =12.74, s.d =5.09) with a small effect size (d=0.3). For the analysis of the Brixton total errors, exclusion of two outliers from the proband group and one outlier in the control group more than doubled effect sizes for comparisons between the clinical and control group. Specifically, comparisons between probands and controls yielded a medium effect size (d=0.5).

ii) Non-eating disorder cotwins vs. control twins

Non-eating disorder cotwins had a higher number of perseverative errors on the WCST in comparison to control twins at trend level with a medium effect size (d=0.4, p=0.12) (see table

7.2). For the analysis of the WCST perseverative errors, exclusion of one outlier in the control group did not largely change the effect size of this group comparison.

For set shifting measured by the Brixton task, non-eating disorder cotwins had a higher number of errors in comparison to controls with a small effect size (d=0.2, p=0.39) at trend level (see table 7.2). For the analysis of the Brixton total errors, exclusion of one outlier in the control group more than doubled the effect size of the comparisons between non-eating disorder cotwins and controls yielding a medium effect size (d=0.53).

Table 7.2: Analysis of Set-Shifting as Associated with Eating Disorders and as Familial Traits

Analysis of the WCST and Brixton task for 'Overall Groups': Probands, Non-ED cotwins and Controls

				Group comparisons, ***Mean difference (95% C.I) p value***	Cohens *d*
	Probands (n=53)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**		
WCST PE[1]	14.75 (11.39)	13.32 (8.33)	10.88 (10.29)	Wald Chi Square: 6.44, df: 2. p= 0.04 Proband > Controls, 0.12 (0.03-0.21) p=0.01 Non-ED cotwin >. Controls, 0.1 (-0.03-0.22) p=0.12	 (d=0.5) (d=0.4)
Brixton errors[2]	12.51 (4.90)	14.16 (6.43)	12.87 (7.46)	Wald Chi Square: 1.07, df: 2. p= 0.59 Proband > Controls, 0.04 (-0.04-0.11) p=0.35 Non-ED cotwin > Controls, 0.04 (-0.05-0.14) p=0.39	 (d=0.2) (d=0.2)

Analysis of the WCST and Brixton task for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

						Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
Specific Diagnosis (NB)	**AN (n=26)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**		
WCST PE[1]	16.46 (13.76)	13.31(8.60)	13 (8.80)	15 (8.25)	10.88 (10.29)	Wald Chi Square: 8.51, df: 4. p= 0.07 AN > Controls, 0.14 (0.01- 0.28) p=0.04 BD > Controls, 0.11 (0.01-0.20) p= 0.03, Non-AN Cotwin > Controls, -0.08 (-0.07- 0.23) p=0.28 Non-BD Cotwin >. Controls, 0.16 (-0.01-0.32) p= 0.07	 (d=0.6) (d=0.4) (d=0.4) (d=0.7)
Brixton errors[2]	12.15 (5.83)	12.62 (3.76)	13.17 (4.24)	15.67 (10.13)	12.87 (7.46)	Wald Chi Square: 2.18, df: 4. P= 0.70 AN > Controls, 0.01 (-0.08- 0.11) p=0.77 BD > Controls, 0.05 (-0.02-0.12) p= 0.18, Non-AN Cotwin > Controls, 0.03 (-0.07- 0.14) p=0.57 Non-BD Cotwin > Controls, 0.05 (-0.11-0.22) p= 0.54	 (d=0.1) (d=0.3) (d=0.2) (d=0.2)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
[1] Means and data analysis for the WCST PE (perseverative errors) were analysed with a log transformation and age included as a covariate (2 d.p)
[2] Means and data analysis for the Brixton errors were analysed with a log transformation and age included as a covariate (2 d.p)

7.6.1.2. Central coherence

Table 7.3 displays the results from the central coherence tasks (ROCF test CCI and GEFT)

i.) Eating disorder twins vs. control twins

Eating disorder probands did not differ from controls on the ROCF CCI (d=0.1, p=0.54). A descriptive comparison showed that those who were currently underweight (n=7, raw mean=1.64, s.d=0.23) had a higher central coherence index than those who were weight recovered (n=46, raw mean =1.32, s.d =0.35) with a large effect size (d=0.9).

Eating disorder probands did not differ significantly from controls on the GEFT median time taken (d=0, p=0.98) (see table 7.3). Stronger local processing was found in AN probands (raw median=12.20, IQR=9.61) with a small effect size (d=-0.3, p=0.32) at trend level. Whereas BD probands (raw median=21.33, IQR=17.27) had weaker local processing in comparison to controls at trend level (d=0.3, p=0.20). A descriptive comparison showed that those who were currently underweight (n=7, raw mean=17.08, s.d=19.63) had a lower median time taken score than those who were weight recovered (n=46, raw mean =19.49, s.d =16.08) with a small effect size (d=0.2).

ii.) Non-eating disorder cotwins vs. control twins

For the ROCF CCI, non-eating disorder cotwins had a significantly lower score in comparison to controls with a medium effect size (d=-0.6, p=0.04) (see table 7.3). For the GEFT median time taken, non-eating disorder cotwins did not differ significantly from controls (d=0.1, p=0.85) (see table 7.3).

Table 7.3: Analysis of Central Coherence as Associated With Eating Disorders and as Familial Traits

Analysis of the ROCF CCI and the GEFT for 'Overall Groups': Probands, Non-ED cotwins and Controls

	Probands (n=53)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**	Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
ROCF CCI[3]	1.36 (0.35)	1.10 (0.41)	1.32 (0.33)	Wald Chi Square: 5.91, df: 2. P= 0.05 Proband = Controls, 0.04 (-0.09-0.18) p=0.54 Non ED cotwin < Controls, -0.22 (-0.42-0.01) p=0.04	 (d=0.1) (d=-0.6)
GEFT median time[4]	13.15 (12.65)	15.85 (12.20)	14.75 (17.33)	Wald Chi Square: 0.05, df: 2. P= 0.98 Proband = Controls, -0.00 (-0.14- 0.13) p=0.98 Non ED cotwin = Controls, 0.01 (-0.13-0.16) p= 0.85	 (d=0) (d=0.1)

Analysis of the ROCF CCI and the GEFT for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

Specific Diagnosis (NB)	**AN (n=26)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**	Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
ROCF CCI[3]	1.42 (0.30)	1.32 (0.38)	1.12 (0.37)	1.03 (0.54)	1.32 (0.33)	Wald Chi Square: 8.57, df: 4. P= 0.07 AN > Controls, 0.11 (-0.05- 0.28) p=0.2 BD = Controls, -0.01 (-0.17-0.19) p= 0.90, Non-AN Cotwin < Controls, -0.19 (-0.41- 0.03) p=0.10 Non-BD Cotwin < Controls, -0.30 (-0.72-0.12) p= 0.16	 (d=0.3) (d=0) (d=-0.6) (d=-0.9)
GEFT median time[4]	12.20 (9.61)	17.33 (25.52)	15.30 (17.98)	21.33 (17.27)	14.75 (17.33)	Wald Chi Square: 5.78, df: 4. P= 0.22 AN <. Controls, -0.08 (-0.24- 0.07) p=0.32 BD > Controls, 0.09 (-0.05-0.24) p= 0.20, Non-AN Cotwin < Controls,- 0.03 (-0.22- 0.16) p=0.77 Non-BD Cotwin > Controls, 0.06 (-0.11-0.24) p= 0.47	 (d=-0.3) (d=0.3) (d=-0.1) (d=0.2)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
[3]Means and data analysis for the ROCF CCI (Central Coherence Index) were analysed with age included as a covariate
[4] Means and data analysis for the GEFT (median time) were analysed with a logarithm transformation and age included as a covariate

7.6.2. Relationships to clinical features

a.) Set-shifting

For eating disorder probands the WCST perseverative errors was positively associated with the OCI-R total score (*r*=0.37, p=0.01) and the OCI-R obsessing (*r*=0.40, p=0.00) and ordering subscales (*r*=0.29, p=0.04), with weak to moderate correlations. It was also positively associated with the EATATE part 2 interview which assessed the need for order and symmetry in childhood (*r*=0.36, p=0.01).

b.) Central coherence

For eating disorder probands stronger local processing (measured by GEFT) was associated with the need for order and symmetry (*r*=0.39, p=0.00**). The ROCF CCI was not significantly associated with clinical features in any of the groups.

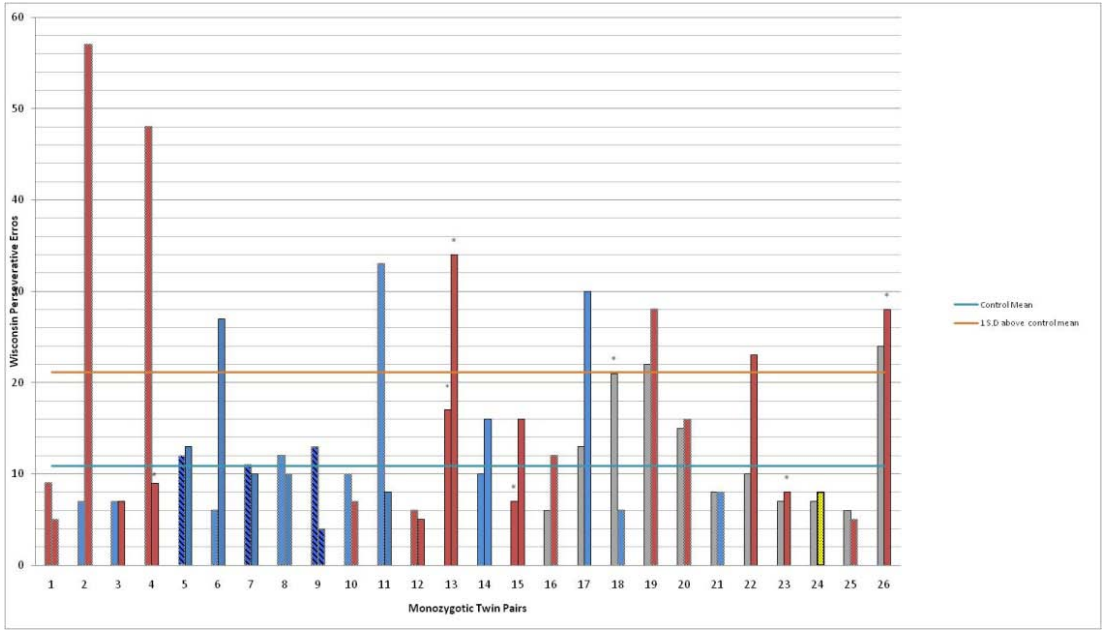
Furthermore, neither age, years of formal education, or current BMI were significantly associated with set shifting or central coherence.

7.6.3 Analysis of neurocognitive traits as heritable

Legend

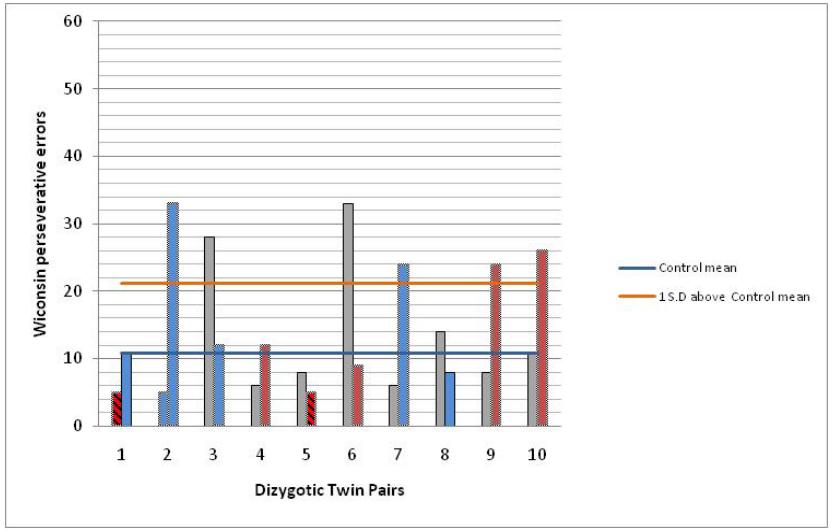
Diagram 7.2: WCST PE in MZ and DZ Twins

Diagram 7.2a: WCST PE Errors in MZ Twin Pairs



Y axis: WCST perseverative errors (PE) (raw score)
X axis: Twin pair (Twin pairs 1 to 15 are concordant for eating disorder diagnosis. Twin pairs 16 to 26 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control mean

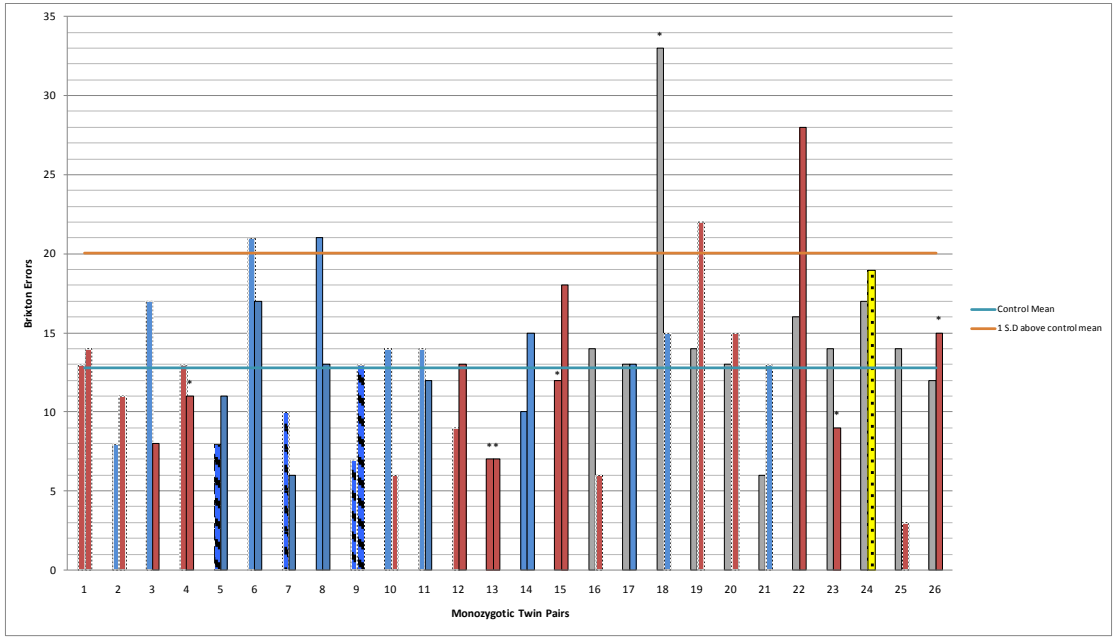
Diagram 7.2b: WCST PE in DZ Twin Pairs



Y axis: Wisconsin Perseverative errors (PE) (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control mean

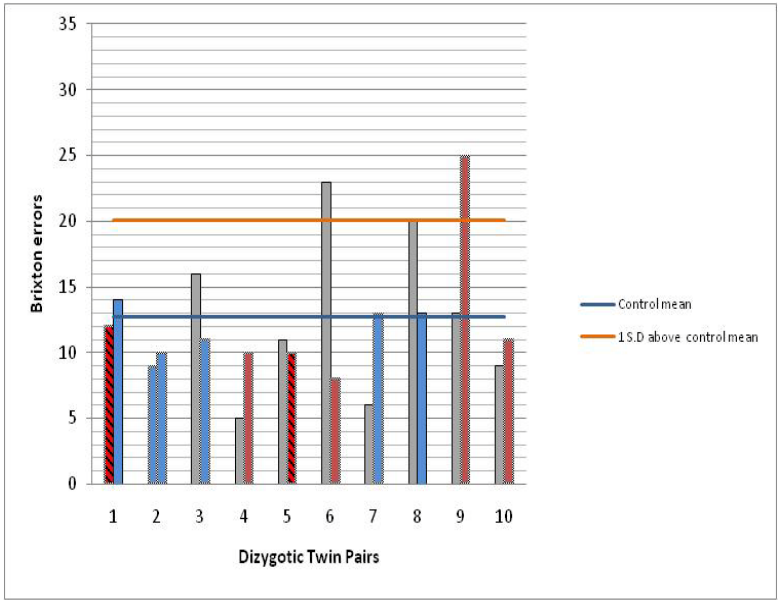
Diagram 7.3: Brixton Errors in MZ and DZ Twins

Diagram 7.3a: Brixton Errors in MZ Twin Pairs



Y axis: Total Brixton errors (raw score)
X axis: Twin pair (Twin pairs 1 to 15 are concordant for eating disorder diagnosis. Twin pairs 16 to 26 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control mean

Diagram 7.3b: Brixton Errors in DZ Twin Pairs



Y axis: Total Brixton errors (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control mean

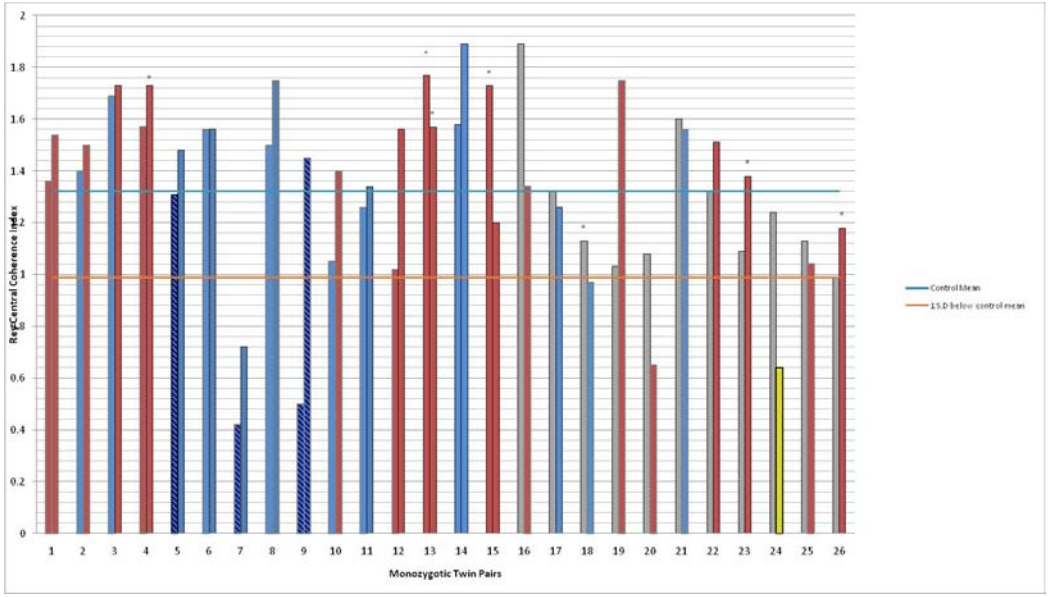
7.6.3.1. Summary of set shifting heritability

An inspection of monozygotic twins in diagram 7.2a shows that some twin pairs are relatively concordant while others have large discrepancies within pairs. For set shifting measured by the WCST the within pair correlation for monozygotic twins was r=-0.02 (CI: -0.39 – 0.37, p=0.53) and r= -0.39 (CI: -0.80 – 0.28, p=0.88) for dizygotic twins. There were two outliers in the proband group. With these outliers excluded for the WCST preservative errors, the within pair correlation for monozygotic twins was r=0.26 (CI: -0.15 – 0.59, p=0.11). Therefore the monozygotic twins indicated more within-pair similarity than dizygotic twins (r= -0.39 CI:-0.80 – 0.28, p=0.88).

For set shifting measured by the Brixton task, the within pair correlations for monozygotic twins was r=0.22 (CI: -0.17 – 0.56, p=0.13) and r=-0.04 (CI: -0.63 – 0.58, p=0.55) for dizygotic twins. There were two outliers in the proband group. With outliers excluded, the within pair correlations for MZ twins was r=0.18 (CI: -0.24 - 0.5, p=0.20) and r=-0.04 (CI: -0.63 – 0.58, p=0.55) for the DZ twins.

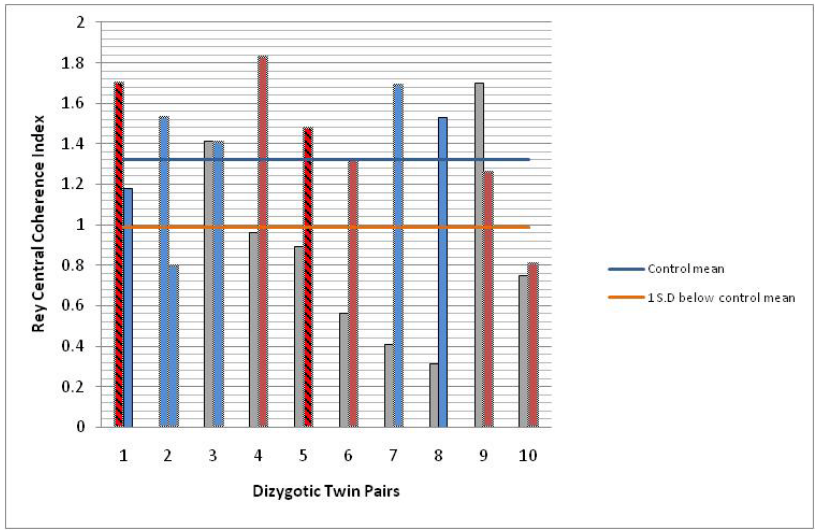
Diagram 7.4: ROCF in MZ and DZ Twin Pairs

Diagram 7.4a: ROCF in MZ Twin Pairs



Y axis: ROCF Central Coherence Index (raw score)
X axis: Twin pair (Twin pairs 1 to 15 are concordant for eating disorder diagnosis. Twin pairs 16 to 26 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control mean

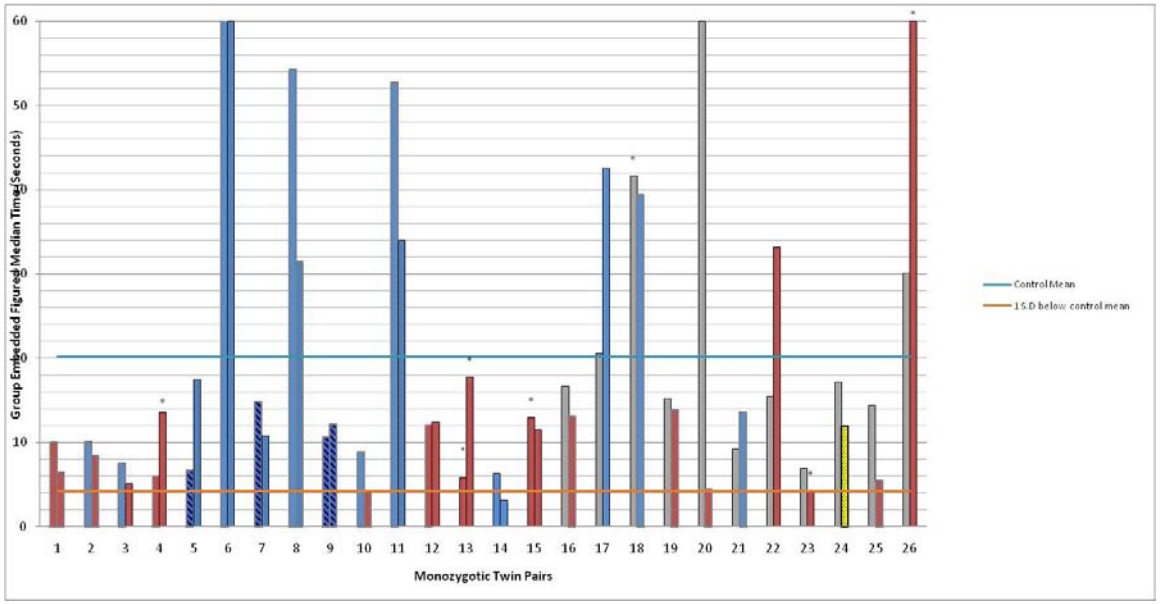
Diagram 7.4b: ROCF in DZ Twin Pairs



Y axis: ROCF Central Coherence Index (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control mean

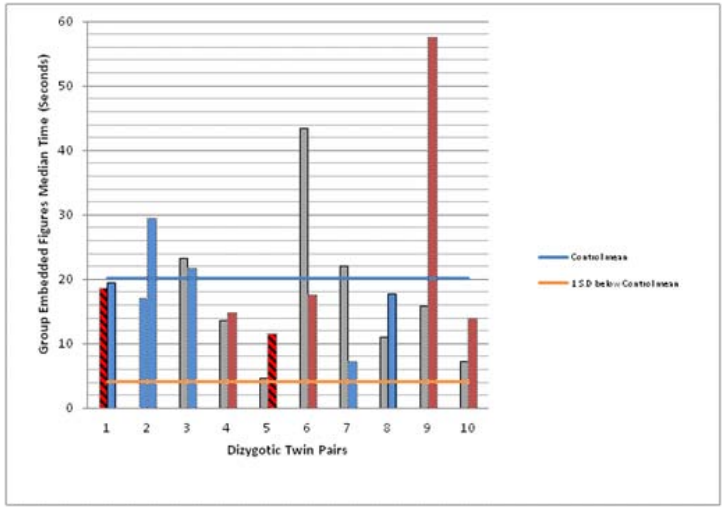
Diagram 7.5: GEFT in MZ and DZ Twins

Diagram 7.5a: GEFT in MZ Twin Pairs



Y axis: Group Embedded Figures Median Time Taken (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control mean

Diagram 7.5b: GEFT in DZ Twin Pairs



Y axis: Group Embedded Figures Median Time Taken (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for eating disorder diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control mean

7.6.3.2 Summary of central coherence heritability

For central coherence measured by the ROCF and GEFT an inspection of monozygotic twins in diagrams 7.4a and 7.5a shows most pairs being relatively concordant in comparison to dizygotic twins depicted in diagrams 7.4b and 7.5b. For the ROCF task, the within pair correlation for monozygotic twins indicated that they were significantly more similar in performance (r=0.44, CI: 0.07-0.70, p=0.01) in comparison to dizygotic twins (r=-0.37, CI: -0.79 – 0.30, p=0.87). Furthermore, for the GEFT within pair correlations for monozygotic twins indicated that they were also significantly more similar in performance (r=0.58, CI: 0.26-0.79, p=0.00) in comparison to dizygotic twins (r=0.18, CI: -0.59 – 0.6,1 p=0.48). Although within pair correlations for dizygotic twins did not reach significance, it may be suggested that with monozygotic twins within pair correlations being more than double that for dizygotic twin pairs for both tasks, this trait is substantially heritable.

7.7 Discussion:

This study explored the genetic basis of set-shifting and central coherence in twins with eating disorders. Both neurocognitive traits were more similar in monozygotic than dizygotic twins, which suggests a genetic contribution. The tests of central coherence in this sample suggested that there was a genetic basis, since within-pair correlations for monozygotic twins were more than double that of dizygotic twins. On the other hand, in the set shifting tasks there was less of a differential correlation between monozygotic and dizygotic twins, suggesting environmental factors may contribute more to these traits. Set shifting difficulties were more marked in people with an eating disorder history and a strength in local processing (measured by the GEFT) was found particularly in those with AN. However, difficulties in global integration (measured by the ROCF CCI) were not found in this group. Impaired set shifting was associated with obsessive compulsive symptoms. In addition, set shifting and central coherence impairments (measured by the ROCF) were more marked in non-eating disorder cotwins of people with an eating disorder history. All of these findings suggest that these traits may be part of the eating disorder endophenotype profile.

7.7.1. Set shifting and central coherence as part of the eating disorder neurocognitive trait profile

Since our probands were a mix of those currently ill and recovered this study investigated the neurocognitive profile as a traitor scar from the illness as opposed to it being exclusively associated with a currently ill status. Performance on the WCST was impaired in probands with medium effect sizes and this was also the case for the Brixton task at trend level, which replicates previous findings (Roberts et al, 2010). People with AN had larger impairments on the WCST task in comparison to BD. Previous research has indicated that this impairment may be more prominent in AN since a recent systematic review has concluded no consistent findings of this measure in those with BD (Van den Eynde et al. 2011). Lastly the presence of these traits in non-eating disorder cotwins lends support to set shifting being a familial trait (Roberts et al. 2010; Tenconi et al. 2010).

People with AN had strengths in local processing (measured by the GEFT) although this was not the case for BD. Overall probands did not demonstrate difficulties in global integration (measured by the ROCF CCI) although the non-eating disorder cotwins group did at trend level. Combining previous findings of the persistence of this trait in recovered AN samples, with the present study's findings of heritability and being a familial trait, it may be concluded that weak coherence is a strong endophenotype in AN (Lopez et al. 2008a; Tenconi et al. 2010).

7.7.2. Set shifting and central coherence as heritable traits

Central coherence appeared to have a more pronounced genetic basis than set shifting in people with eating disorders. This is similar to what was found in ADHD, a disorder associated with eating disorders, where set shifting (measured by the Wisconsin Perseverative errors) was found to be less heritable (0.18) than central coherence (0.27, measured by the ROCF CCI) in a study of family trios (Biederman et al. 2007; Doyle et al. 2008). Research into control samples have also found variation in the WCST performance to be largely accounted for by unique environment (69%) and shared environmental factors (31%) (Chou et al. 2010; Campana et al. 1996; Kremen et al. 2007, Nicole and Del Miglio, 1997; Taylor, 2007). Possible environmental factors accounting for the variance may range from not understanding the experimental instructions to the physical effects of starvation.

7.7.3. Limitations

The study has several shortcomings, which are worth highlighting. Firstly, the limited sample size means that this study is exploratory.

Secondly, our relatively mixed sample of BN and BED (47.2%) and almost equal proportion of AN (52.8%) is taken into account when interpreting the findings. At present the neurocognitive profile of BED has received less investigation and a recent review has found no consistent profile in BN (Van den Eynde et al. 2011). Further research is clearly needed to determine traits that characterise these disorders.

Thirdly, more monozygotic twins were currently ill (i.e. 56.1% recovered) in comparison to dizygotic twins (83.3% recovered), which may have influenced the analysis of heritability. Nevertheless, the number of probands that were currently underweight (BMI< 18.5) were only marginally greater in the monozygotic group (14.6 %) in comparison to the dizygotic (0%) group. Fourthly, using a volunteer twin registry is another potential source of sampling bias, since it requires that the twins contact the registry themselves. Thus those that are more invested in being a twin may be more likely to volunteer (Bulik et al. 2000). This also makes it unlikely that twin pairs who have a less close relationship will participate and hence limits the generalisability of our results.

Fifthly, the ascertainment of participants differed from previous studies that have recruited from inpatient units. Only 41.5% had received treatment and 64% were recovered. Those that never reach the attention of hospital services represent an understudied group. In addition those that recover from eating disorders may represent a different class of the disorder to those that remain chronically ill.

Sixthly, the non-eating disorder cotwins comparatively older age may have contributed to findings in this group, since neurocognitive impairments are known to increase with age (Ridderinkhof et al. 2002; Ardila et al. 2000). Additional data such as the delay and accuracy aspects of the ROCF may have added important details to this study, although these were excluded from the protocol at the outset to reduce the burden on participants. Nevertheless, the similarity within monozygotic twins validates the external validity of the neuropsychological tasks. However the presence of frequent outliers observed in the WCST and Brixton task, which may have resulted because of poor engagement, suggests that these tasks may not be robust measures.

Seventhly, in this study we chose not to exclude those with depression in our clinical sample, due to the restraints of our sample size and this being a common comorbidity in eating disorders. However, it is well acknowledged that depression can amplify deficits in neurocognitive function and this may have influenced our findings (Gotlib and Joorman, 2010; McClintock et al. 2010).

7.8. Conclusions

The present study set out to explore whether aspects of the neurocognitive profile associated with eating disorders could be considered as endophenotypes using a variety of methods. Preliminary support was found for set-shifting and central coherence endophenotype status. Both traits, especially central coherence appear to be heritable. Furthermore set shifting difficulties are elevated in eating disorders and associated with OCD symptoms. Lastly, both set shifting difficulties and weak central coherence are found in their unaffected twin siblings. Combining these findings lends support to poor set shifting and weak central coherence being intermediate traits that lie between clinical symptoms and the genes that confer risk. Future studies with larger samples and those adopting longitudinal designs are required to explore and confirm the present study's findings.

8. Chapter 8: Emotional Processing as a Behavioural Endophenotype in Eating Disorders: A Preliminary Investigation in Twins

8.1 Introduction to the chapter

This chapter describes the sixth experimental study of this thesis. It explores whether emotional processing might be considered as a potential endophenotype in eating disorders. Previous research (Harrison et al 2010c) has indicated that difficulties in emotional processing is present post recovery and therefore independent of the active illness state. This suggests that they may be premorbid genetic risk factors.

To gather evidence of its potential endophenotype status, the criteria for a familial and genetic risk as outlined by Gottesman and Gould (2003) were investigated. This hopes to inform the direction of genetic and environmental contributions to these traits.

8.2 Background and development of the study

People with EDs commonly have difficulties in social and emotional functioning (Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c; Zucker et al 2007; Oldershaw et al. 2010). As detailed in the introduction (chapter 1, section 1.19), research has found that people with EDs (AN and BN) have difficulties in emotion recognition [measured by the reading the mind in the eyes task (RME); Baron-Cohen, et al 2001] (Russell et al 2009; Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c; Oldershaw et al 2010), abnormal attention to social threat [measured by the emotional stroop task (Estroop); Ashwin et al 2006] (Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c) and difficulties in emotion regulation [measured by the Difficulties in Emotion Regulation Scale (DERS) Gratz and Roemer 2003] (Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c). Furthermore the persistence of these traits in people who have recovered from AN suggests that they are not just a consequence of the depressive and anxious symptomatology that is present in the acute state but may be endophenotypes arising from a genetic vulnerability (Gottesman and Gould 2003). The literature in other psychiatric conditions such as autistic spectrum disorders (Losh and Piven 2007; Baron Cohen et al 1997) and schizophrenia (de Achaval et al 2009; Ibanez et al 2010) suggests that emotion recognition difficulties measured by the RME task may be a familial trait that is present in unaffected first degree relatives. At present the familial and genetic risk of these traits in ED samples is yet to be investigated. This will form the focus of the present chapter.

8.3 Aims

The aim of this study was to explore whether emotional processing might be considered as an endophenotype in eating disorders using a genetically sensitive design (a twin study). Three

endophenotype criteria outlined by Gottesman & Gould (2003) were investigated: a) the association of difficulties in emotion recognition, attention; bias to social stimuli and difficulties in emotion regulation, with EDs, b) co-segregation within families and c) heritability.

8.4 Hypotheses

The main hypothesis was that people with eating disorders would have difficulties in emotional processing and investigations into their twin siblings would indicate that these are familial and genetic risks factors.

8.4.1 Objectives and specific predictions:

According to previous literature the following objectives were outlined and predictions were made:

The first objective was to examine the association between emotional processing difficulties and the illness, by comparing people with eating disorders with controls. It was hypothesised that people with eating disorders would have difficulties in emotional processing in comparison to controls.

The second objective was to investigate difficulties in emotional processing as predictors of specific eating disorder symptoms in probands. It was hypothesised that greater levels of difficulties in emotional processing would be associated with more severe and chronic symptoms.

The third objective was to assess co-segregation within families, by examining the presence of these traits in non-eating disorder cotwins. It was hypothesised that non-eating disorder cotwins would show difficulties in emotional processing in comparison to controls.

The fourth objective was to examine heritability by comparing monozygotic and dizygotic twins. It was hypothesised that emotional processing would be more similar within monozygotic twin pairs in comparison to dizygotic twin pairs.

8.5 Methods

8.5.1 Study design

As described in detail in chapter 3, a familial design (section 3.15.5) was employed to assess non-eating disorder cotwins in comparison to controls and lastly a twin design (section 3.15.6) was employed to assess the genetic risk of emotional processing difficulties.

8.5.2 Participants

Participants were the clinical and control twin groups described in chapter 3 (section 3.10). From this sample one concordant monozygotic twin pair was excluded since they were unable to take part in the present study. Therefore the present sample included 25 monozygotic twin pairs and 10 dizygotic twin pairs where at least one had an eating disorder history as defined by the DSM-IV (APA, 2000). The control group included a total of 42 twins.

8.5.3 Materials:

8.5.4 Clinical assessment

The EATATE semi structured interview was administered to all probands and non-eating disorder cotwins (Anderluh et al 2003). All participants also completed the NART (Nelson and Wilson 1991) as an indication of premorbid IQ, the OCI-R (Foa et al 1991) to assess obsessive compulsive symptoms, the DASS (Lovibond and Lovibond, 1995) to assess depression and anxiety and the Rosenberg Self-esteem measure (Rosenberg, 1984). The aforementioned measures are described in greater detail in chapter 3 (section 3.6).

8.5.5. Personality assessment

8.5.5.1 Difficulties in emotion regulation scale (DERS) (Gratz and Roemer, 2004).

The DERS is a 36 item assessment of emotion regulation (see appendix 1.13). Participants are asked to indicate how often each statement applies to them, ranging from 1 (0-10% of the time) to 5 (91-100% of the time). The scale results in a total score, which is the sum of all the items with higher scores indicating greater difficulties in emotion regulation. The scale can be divided into six subscales which are distinct yet related. These include:

- ‘Non acceptance’ (non acceptance of emotional responses) which is comprised of items assessing the tendency to have negative secondary emotional responses to negative emotions. It also assesses non acceptance of emotional distress.
- ‘Goals’ (difficulties engaging in goal directed behaviour) which is composed of items assessing difficulties in concentrating or completing tasks when experiencing negative emotions.
- ‘Impulse’ (impulse control difficulties) which is comprised of items assessing difficulties in controlling behaviour when experiencing negative emotions.
- ‘Awareness’ (lack of emotional awareness) which is composed of items reflecting the tendency to acknowledge emotions. After being reverse scored it assesses a lack of awareness and inattention to emotion.

- ‘Strategies’ (limited access to emotion regulation strategies) which assesses the frequency of the belief that once the person has become upset there is little that can be done to regulate emotions effectively.
- ‘Clarity’ which assesses the extent to which the person is clear about the emotion they are experiencing.

Gratz and Roemer (2004) determined that the psychometric properties of the DERS were excellent in a sample of 357 male and female controls aged 23.10 (S.D=5.67). The DERS had a high internal consistency (Cronbachs alpha = 0.93), indicating that all the items measure the same latent variable. The measure also demonstrated good construct validity since it was negatively correlated (r=-0.69**) with the self-regulation of negative moods (measured by the Generalized Expectancy for Negative Mood Regulation Scale; Catanzaro & Mearns, 1990), emotional expression (measured by the Emotion Expressivity Scale; Kring, Smith, & Neale, 1994) and experiential avoidance (measured by the Acceptance and Action Questionnaire; Hayes et al 2004). This supports that the DERS measures the psychological construct that it set out to. The DERS demonstrated good predictive validity since it was significantly positively correlated with self-harm in men (r=0.26**) and women (r=0.20**). Furthermore it was positively correlated with intimate partner abuse in men (r=0.34**). Lastly, the test-retest reliability from 4 to 8 weeks was good (p=0.88, p<0.01) suggesting low measurement error and the sensitivity to detect subtle changes over time.

8.5.5.2 Behavioural inhibition system and behavioural activation system scales (BIS/BAS scales; Carver and White, 1994)

The BIS/BAS is a 20-item questionnaire designed to assess two general motivation systems of behaviours and affect (see appendix 1.14). The behavioural inhibition scale (BIS) assesses punishment sensitivity and includes items such as ‘I worry about making mistakes’. Behavioural activation is assessed using 3 related scales. The BAS drive scale assesses the persistent pursuit of desired goals. The BAS fun seeking scale assesses the desire for new rewards and the BAS reward responsiveness scales assesses the focus on positive response in the anticipation of reward. The scores are totalled for each subscale. Participants are required to respond to each statement using a 4-point likert scale ranging from 1 (‘very true for me’) to 4 (‘very false for me’). In our sample Cronbachs alpha was 0.75 for the BIS, 0.79 for the BAS reward responsiveness, 0.82 for the BAS drive and 0.81 for the BAS fun seeking scale.

8.5.5.3 Appetitive motivation scale (AMS Jackson and Smillie, 2004)

The AMS is an 11-item measure of reward reactivity (see appendix 1.15). Participants are required to indicate to what extent they agree with each statement using a 4 point likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). The statements include items such as ‘I

actively look for new experiences ‘The final score is the total of the items. In Jackson and Smillie’s (2004) sample the Cronbachs alpha was 0.83 for the full scale indicating adequate internal consistency. In this sample Cronbachs Alpha was 0.77.

8.5.6 Behavioural assessment: measures of emotional processing

All participants were administered the Emotional Stroop Task (Ashwin et al 2006) which was used to assess social and angry threat attentional biases and the Reading the Mind in the Eyes task (revised; Baron-Cohen et al., 2001) that was used to assess emotion recognition.

8.5.6.1 Reading the mind in the eyes task, (Baron-Cohen, Wheelwright, Hill, Raste and Plumb (2001)

This task is a measure of complex emotion recognition. At the beginning of the task, participants are presented with a practice, which also acts as a control. They are presented with 10 slides of sets of eyes and asked to indicate whether they are male or female (see appendix 1.16). Subsequently participants are presented with 36 slides of sets of eyes belonging to males and females on a computer screen. Each picture of eyes was a standardised size, in black and white, depicting the face from the brow down to the nose midway. On each slide surrounding the eyes are four words describing cognitive mental states each indicating what the person in the picture may be thinking or feeling. Participants are required to indicate which of the words bear the closest resemblance to the eyes. They are provided with a booklet containing all the word definitions which they can refer to at any time. Furthermore participants are allowed to move through the slides at their own pace and they are told that there is no time limit for this task. The outcome measure is the percentage of correct answers with lower scores indicating greater difficulties in recognising emotions.

This task is suggested to be an advanced pure theory of mind test. This is because the task does not require executive functions such as attention switching, planning or inhibition. Furthermore the slides do not provide contextual information so it does not entail a central coherence component. This enables theory of mind abilities to be assessed without the confounding variables (Baron-Cohen, Jolliffe, Mortimore and Robertson, 1997). The task has good test-retest reliability (Hallerback, Lugnegard, Hjarthag and Gillberg, 2009). Furthermore performance on this task is reflective of other tasks also testing advanced theory of mind abilities [Happé (Strange Stories), 1997; Baron-Cohen, Jolliffe, Mortimore and Robertson, 1997].

8.5.6.2. Pictorial emotional stroop task (Ashwin, Wheelwright and Baron-Cohen (2006)

This is a computerised task, developed by Ashwin and colleagues (2006) and designed to measure involuntary attentional biases to social stimuli and angry faces. It is proposed that attentional bias is the result of facial stimuli being harder to interpret in comparison to non-social stimuli. Facial pictures for this task were taken from a standard set (Lundqvist et al. 1998, see appendix 1.17). The basic emotion depicted by each picture, (afraid, angry, sad, happy, surprise, disgust and neutral) were judged by a panel of 5 males and 5 female judges. This resulted in a selection of 6 male and 6 female pictures with angry or neutral expressions. For the non-social control stimuli a picture of a chair was downloaded from the internet. The same crop outline used for the faces were also used for the pictures of chairs. All the pictures were tinted with one of four colours; red, blue, green or yellow. Throughout the main task the participant is presented with 48 neutral faces, 48 threat faces, both of which include an equal number of male and female faces and 48 pictures of chairs. The pictures from all 3 conditions are presented in a randomised order in 3 blocks of 48, with two rest periods in between. Therefore the participants are presented with a total of 144 trials.

Before the main task the participant undergoes 8 practice trials to ensure that the instructions are understood and that their voice can be detected by the microphone. At the beginning of the task, participants are instructed to name the colour of the picture they see as quickly as possible. For the main task the participant is presented with each stimulus once, for a maximum of 4000ms. Response times are recorded using DMDX software (Forster and Forster, 2003). Trials where the participant does not respond are removed from the mean response time. Two outcome variables are derived using the response latency of the participants' response, rather than the accuracy (see section 8.6.1).

8.5.7 Procedure:

Participants were interviewed by a trained researcher using the EATATE semi-structured interview (Anderluh et al 2003) (chapter 3, section 3.5.3). Demographics and self report measures were completed and obtained on the day of testing. Tasks were administered in the following order: Estroop (Ashwin et al 2006) and the RME (Baron Cohen et al 1997). The DERS (Gratz and Roemer, 2004; section 8.5.5.1), AMS (Jackson and Smillie, 2004; section 8.5.5.3) BIS/BAS (Carver and White, 1994; section 8.5.5.2) and DASS (Lovibond and Lovibond, 1995, section 3.6.1) self report measures were administered to all participants.

8.6 Statistical methods

8.6.1 Construction of attentional bias variables

The social attentional bias variable is derived by subtracting the mean response time to colour name all the social stimuli, (which include the male and female, angry and neutral faces) from the mean response time to colour name all the non social stimuli (chairs). Positive numbers indicate social attentional bias and higher scores are indicative of stronger social attentional bias.

The attentional bias to angry faces is derived by subtracting the mean response time to colour name male and female angry faces, from the mean response time to colour name neutral faces. Positive numbers indicate attentional bias to angry threat stimuli and higher numbers indicate a stronger attentional bias to angry faces.

8.6.2 Statistical analysis

The statistical procedures applied are those described in chapter 3 (section 3.15).

8.6.3 Sample size and power

The sample size in the present study was limited by the number of twins it was possible to recruit with the resources available. Due to the exploratory nature of this study a post hoc power analysis was conducted using GPower software. This indicated that the present sample would have 66%, 97%, 100% and 100% power for detecting group differences between probands and controls at the 0.05 level for the RME, Estroop social attentional bias, angry attentional bias and DERS measures respectively (based on Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c).

8.7 Results

8.7.1. Analysis of emotional processing traits as associated with eating disorders and as familial traits

i) ED twins vs. control twins

For emotion recognition measured by the RME task, probands had less accuracy in comparison to controls with a small effect size (d=-0.1) at trend level (Table 8.1). This impairment was more pronounced in AN probands at trend level (small sized effect; d=0.3) in comparison to BD probands where there was no difference in comparison to control twins (d=0) (Table 8.1). A descriptive comparison showed that those who were currently underweight (n=6, raw mean=74.79, s.d=10.36) were no different (d=0.01) to those who were weight recovered (n=45, raw mean =75.43, s.d =10.51) in emotion recognition measured by the RME.

For attentional bias measured by the Estroop, probands had a greater social attentional bias (d=0.2) at trend level and a significantly greater angry threat attentional bias (d=0.5) in comparison to control twins. AN and BD probands had the same level of social attentional biases (d=0.2). However the attentional bias to anger was more pronounced in BD probands (d=0.7) than AN probands (d=0.3) (Table 8.2 and 8.3).

A descriptive comparison showed that those who were currently underweight (n=6, raw mean=1896.08, s.d=135.41) had a greater social attentional bias in comparison to those who were weight recovered (n=45, raw mean =13.97, s.d =67.69) with a huge effect size (d=24.82). Furthermore those who were currently underweight (n=6, raw mean=-14.65, s.d=21.71) had less angry attentional bias in comparison to those who were weight recovered (n=45, raw mean =2020.53, s.d =357.0) with a large effect size (d=6.14).

For the DERS, ED probands had a significantly higher score in comparison to control twins with a very large effect size (d=1.1) and BD (d=1.2) and AN (d=1.2) probands had similar levels of difficulties (Table 8.4).

ii) Non-ED cotwin vs. control twins

For emotion recognition measured by the RME task, non-ED cotwins had less accurate scores in comparison to control twins with a small effect size (d=-0.1) at trend level (Table 8.1).

For attentional bias to social stimuli measured by the Estroop, non-ED cotwins did not differ from control twins (d=0.0). In the condition assessing attentional bias to angry stimuli there was an attentional bias in the opposite direction; towards neutral stimuli at trend level (d=-0.3) (Table

8.3). There appeared to be opposite effects between diagnoses, in that non-BD cotwins had a greater attentional bias to angry stimuli in comparison to controls (d=0.6), whereas non-AN cotwins had a greater attentional bias to neutral stimuli (d=-0.9) (Table 8.3).

For the DERS, non-ED cotwins overall had a significantly higher score in comparison to controls with a medium effect size (d=0.6). Specifically non-AN cotwins (d=0.8) had a significantly higher score in comparison to controls whereas non-BD cotwins (d=0.3) only differed from controls at trend level (Table 8.4).

Table 8.1: Analysis of Emotion Recognition Measured by the RME as Associated Eating Disorders and as a Familial Trait

Analysis of the RME for 'Overall Groups': Probands, Non-ED cotwins and Controls

RME (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***[1]	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**		
RME % correct[1]	75.4 (10.4)	74.5 (8.2)	76.1 (9.2)	Wald Chi Square: 0.39, df: 2. p= 0.82	
				Proband < Control twins , -1.24 (5.31-2.82) p=0.55	(d=-0.1)
				Non-ED cotwin < Control twins, -1.03 (-5.68-3.62) p=0.67	d=-0.1)
				Probands = Non-ED cotwins,-0.22 (-4.68-4.24) p=0.92	(d=-0.0)

Analysis of the RME for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

RME (Raw Scores)						Group comparisons, ***Mean difference (95% C.I) p value***[1]	Cohen's *d*
Specific Diagnosis (NB)	**AN (n=24)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**		
RME % correct[1]	74.9 (10.1)	76.4 (10.8)	74.1 (8.4)	73.9 (8.5)	76.1 (9.2)	Wald Chi Square: 2.86, df: 4. p= 0.58	
						AN < Control twins, -2.93 (-7.72-1.86) p=0.23	(d=-0.3)
						BD = Control twins, 0.05 (-4.71-4.81) p= 0.98	(d=0)
						Non-AN Cotwin < Control twins, -1.14 (-7.03- 4.74) p=0.70	(d=-0.1)
						Non-BD Cotwin < Control twins, -2.47 (-7.74-2.80) p= 0.36	(d=-0.2)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge-purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS-BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the RME % correct were analysed with age included as a covariate

Table 8.2: Analysis of the Estroop Social Attentional Bias as Associated with Eating Disorders and as a Familial Trait

Analysis of the Social Attentional Bias for Overall Groups': Probands, Non-ED cotwins and Controls

Estroop social attentional bias (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***[1]	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins (42)**		
Estroop social attentional bias[1]	2005.3 (339.3)	1991.1 (235.4)	1969.2 (283.2)	Wald Chi Square: 0.39, df: 2. p= 0.82	
				Proband > Control twins, 48.03 (-79.98-176.04) p=0.46	(d=0.2)
				Non-ED cotwin < Control twins -10.67 (-141.63-120.30) p=0.8	(d=-0.0)
				Probands = Non-ED cotwins -58.70 (-75.95-193.35) p=0.39	(d=0.0)

Analysis of Social Attentional bias for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

Estroop social attentional bias (Raw Scores)						Group comparisons, ***Mean difference (95% C.I) p value***[1]	Cohen's *d*
Specific Diagnosis (NB)	**AN (24)**	**BD (26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (42)**		
Estroop social attentional bias[1]	1976.5 (300.7)	2036.5 (384.5)	1980.1 (222.8)	1994.1 (295.4)	1969.2 (283.2)	Wald Chi Square: 2.33, df: 4. p= 0.68	
						AN > Control twins, 52.56 (-100.49-205.60) p=0.50	(d=0.2)
						BD > Control twins, 88.66 (-54.67-231.98) p= 0.23	(d=0.2)
						Non-AN Cotwin > Control twins, 24.75 (-172.41-122.90) p=0.74	(d=0.1)
						Non-BD Cotwin = Control twins, 11.29 (-216.03-238.62) p= 0.92	(d=0)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis
Proband: Monozygotic probands, dizygotic probands
Non ED Cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge-purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS-BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non bulimic disorder cotwins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the estroop social attentional bias were analysed with age included as a covariate

Table 8.3: Analysis of the Estroop Angry Attentional Bias as Associated with Eating Disorders and as a Familial Trait

Analysis of the Angry Attentional Bias for 'Overall Groups': Probands, Non-ED Cotwins and Controls

Estroop angry attentional bias (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**		
Estroop angry attentional bias[1]	10.5 (64.4)	-32.4 (79.0)	-14.6 (55.5)	Wald Chi Square: 6.9, df: 2. p= 0.03	
				Proband > Control twins, 27.59 (2.00-53.17) p=0.04	d=0.5)
				Non-ED cotwin < Control twins, -18.99 (-56.96-18.97) p=0.33	(d=-0.3)
				Probands > Non-ED cotwins, 46.58 (6.1-86.66) p=0.02	(d=0.7)

Analysis of the Angry Attentional Bias for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

Estroop angry attentional bias (Raw Scores)						Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
Specific Diagnosis (NB)	**AN (n=24)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**		
Estroop angry attentional bias[1]	-1.4 (49.1)	22.9 (77.0)	-65.6 (77.0)	18.2 (43.7)	-14.6 (55.5)	Wald Chi Square: 17.99, df: 4. p= 0.0	
						AN > Control twins, 16.71 (8.13-41.54) p=0.19	(d=0.3)
						BD > Control twins, 41.54 (5.66-77.42) p= 0.02	(d=0.7)
						Non-AN Cotwin < Control twins, -54.99 (-98.35-11.65) p=0.01	(d=-0.9)
						Non-BD Cotwin > Control twins, 29.74 (-7.75-65.23) p= 0.12	(d=0.6)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non ED Cotwin: Monozygotic and dizygotic non eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non bulimic disorder cotwins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the estroop angry attentional bias were analysed with age included as a covariate

Table 8.4: Analysis of DERS as Associated with Eating Disorders and as a Familial Trait

Analysis of the DERS for 'Overall Groups': Probands, Non-ED Cotwins and Controls

DERS total score (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**		
DERS total score[1]	94.6 (30.0)	82.5 (24.5)	68.3 (16.7)	Chi Wald Square=23.49, df=2, p=0.00	
				Proband > Control twins , 26.58 (15.78-37.38) p=0.00	(d=1.1)
				Non ED cotwin > Control twins, 11.81 (-0.79-24.42) p=0.04	(d=0.6)

Analysis of the DERS for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

Specific Diagnosis (NB)	**AN (n=24)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**	Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
DERS total score[1]	95.1 (29.4)	94.2 (31.2)	84.6 (30.7)	80.8 (20.7)	68.3 (16.7)	Chi Wald Square=25.78, do=4, p=0.00	
						AN > Control twins, 26.44 (13.72-39.17) p=0.00	(d=1.2)
						BD > Control twins, 26.96 (13.59-40.33) p= 0.00	(d=1.2)
						Non-AN Cotwin > Control twins, 15.58 (1.02-30.14) p=0.04	(d=0.8)
						Non-BD Cotwin > Control twins, 5.08 (-16.13-26.29) p= 0.64	(d=0.3)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED Cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge-purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS-BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the DERS total scores were analysed with age included as a covariate

8.7.2. Relationship of emotional processing to clinical features

a) Emotion recognition

There were no significant associations between clinical features and emotion recognition in any of the groups.

b) Social and angry attentional bias

For probands, greater social attentional bias (measured by the Estroop) was positively associated with the duration of bingeing (r=0.36, p=0.01) and a greater social attentional bias (measured by the Estroop) was associated with lower levels of BAS reward responsiveness (r=-0.34, p=0.01). Social attentional bias was not significantly associated with any features in non-ED cotwins or control twins.

c) DERS

In probands, the DERS was positively related to the BIS with a medium sized association (r=0.61, p=0.00). In control twins, the DERS was positively associated with the AMS total score (r=0.43, p=0.01) and negatively associated with the BAS fun seeking subscale (r=-0.40, p=0.01).

8.7.3 Analysis of emotional processing traits as heritable

Legend

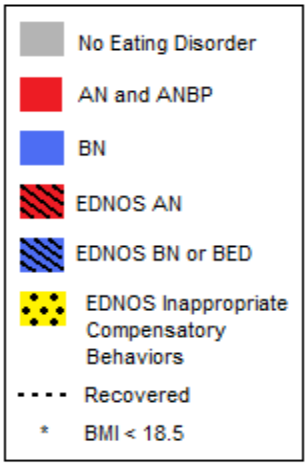
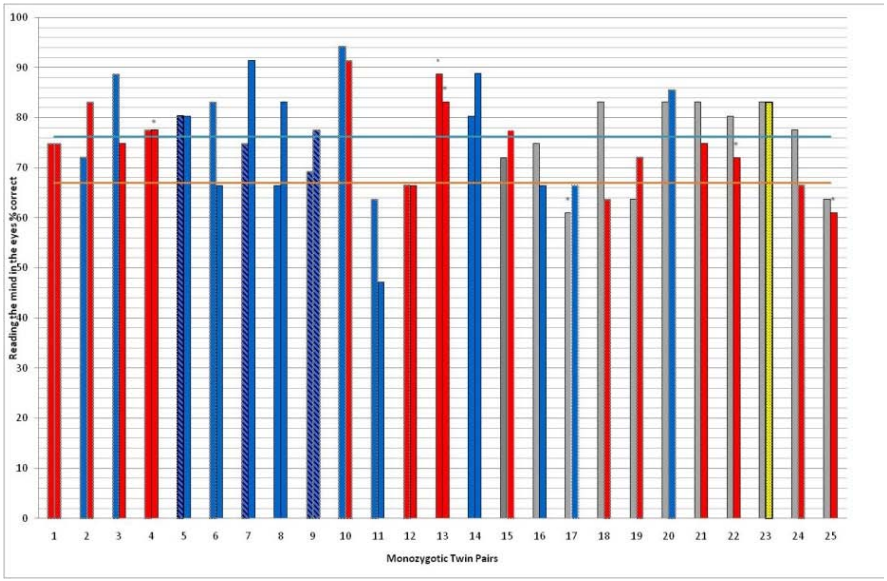


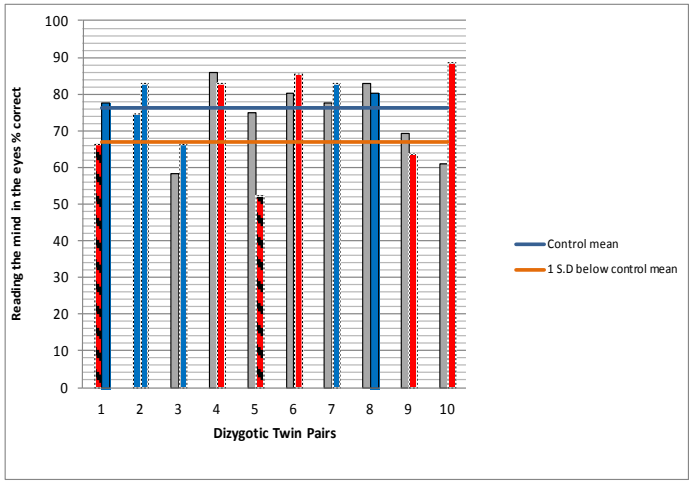
Diagram 8.1: Emotion Recognition in MZ and DZ Twins

8.1a: Emotion Recognition in MZ Twin Pairs



Y axis: RME % correct (raw score)
X axis: Twin pair (Twin pairs 1 to 14 are concordant for ED diagnosis. Twin pairs 15 to 25 are discordant with twin 2 indicating the proband)
1 S.D below control mean - 1 standard deviation below control twin mean

8.1b: Emotion Recognition in DZ Twin Pairs



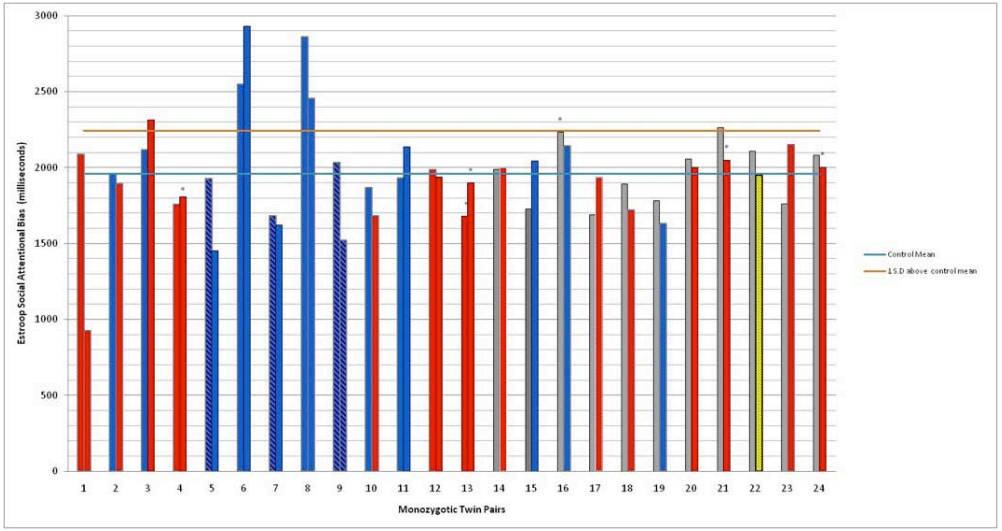
Y axis: RME % correct (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for ED diagnosis. Twin pairs 3 to 10 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control twin mean

8.7.3.1. Summary of emotion recognition as heritable

A visual inspection of diagrams 8.1a and 8.b suggests that monozygotic twins demonstrate greater within pair similarity than dizygotic twins. Although within pair correlations for dizygotic twins did not reach significance, monozygotic within pair correlations [r=0.47 (CI: 0.1-0.74) p=0.01] were more than double that for dizygotic twins [r=0.24 (CI: -0.43-0.73) p=0.24], suggesting that this trait might be substantially heritable.

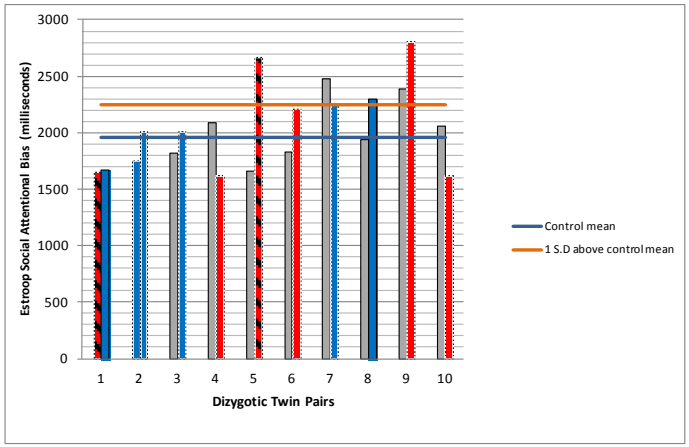
Diagram 8.2: Social Attentional Bias in MZ and DZ Twins

8.2a: Social Attentional Bias MZ Twin Pairs



Y axis: Estroop social attentional bias (milliseconds) (raw score)
X axis: Twin pair (Twin pairs 1 to 13 are concordant for ED diagnosis. Twin pairs 14 to 24 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control twin mean

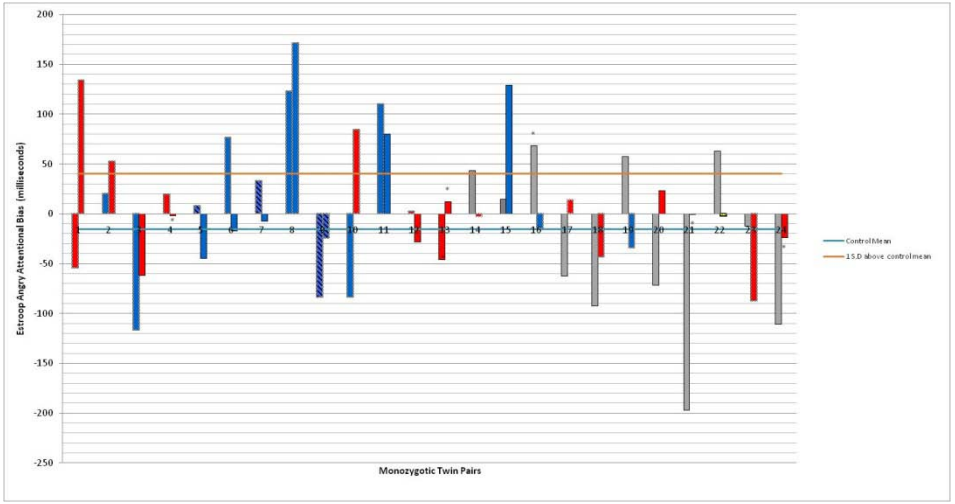
8.2b: Social Attentional Bias in DZ Twin Pairs



Y axis: Estroop social attentional bias (milliseconds) (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for ED diagnosis. Twin pairs 2 to 10 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control twin mean

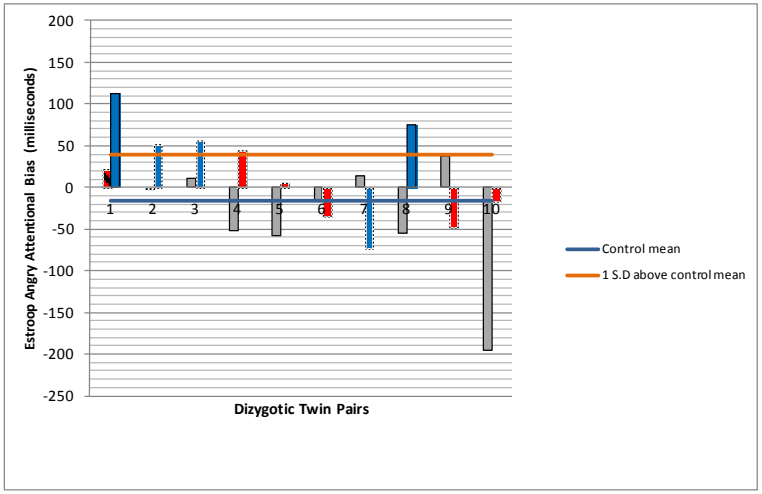
Diagram 8.3: Angry Attentional Bias in MZ and DZ Twins

8.3a: Angry Attentional Bias in MZ Twin Pairs



Y axis: Estroop angry attentional bias (milliseconds) (raw score)
X axis: Twin pair (Twin pairs 1 to 13 are concordant for ED diagnosis. Twin pairs 14 to 24 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control twin mean

8.3b: Angry Attentional Bias DZ Twin Pairs



Y axis: Estroop angry attentional bias (milliseconds) (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for ED diagnosis. Twin pairs 2 to 10 are discordant with twin 2 indicating the proband)
1 S.D above control mean- 1 standard deviation above control twin mean

8.7.3.2 Summary of emotion attentional bias as heritable traits

A visual inspection of diagrams 8.2a and 8.2b suggests that most monozygotic twins are relatively concordant in comparison to dizygotic twins for social attentional bias measured by the Estroop. It may be suggested that with monozygotic within pair correlations [r=0.48 (CI: 0.11-0.74; p=0.01)] being more than double that for dizygotic twins [r=0.21, (CI: -0.45-0.72) p=0.03], this trait is substantially heritable.

A visual inspection of diagrams 8.3a and 8.3b indicates wide variation in angry attentional bias across the twins and within pairs. Nevertheless MZ twins [r=0.25 (CI: -0.16-0.59) p=0.11] had marginally greater within pair similarity than DZ twins [r=0.06 (CI: -0.56-0.64) p=0.43].

8.7.3.3 Summary of the DERS as heritable traits

The monozygotic within pair correlation [r=0.30 (CI: -0.11-0.62) p=0.08] for the DERS was not higher than the dizygotic within pair correlation [r=0.67 (CI: 0.01-0.93) p=0.02] suggesting a stronger influence of non-genetic factors.

8.8 Discussion

The aim of this study was to explore aspects of emotion processing [Emotion recognition measured by the RME task (Baron-Cohen et al 2001), attentional biases to social and threat stimuli measured by the Estroop (Ashwin et al 2001) and difficulties in emotion regulation measured by the DERS (Gratz and Roemer 2003)] as endophenotypes using a genetically sensitive design (a twin study). The participants varied in terms of age, diagnosis, symptoms, and stage of the illness. The first criteria, for the endophenotypes to be associated with the illness were met for all the measures at a minimum trend level. Two of these traits; angry attentional bias (measured by the Estroop) and difficulties in emotion regulation (measured by the DERS) were found in the unaffected cotwins at a minimum trend level, suggesting that they co-segregate within families. Lastly, emotion recognition and social attentional biases appeared to have substantial heritability.

In the present sample, AN probands demonstrated greater difficulties in emotion recognition measured by the RME, with a small effect size (d=-0.3). The size of the effect in the meta-analysis conducted by Oldershaw and colleagues (2010) was medium; d=-0.51 (95% CI -0.73 to -0.28). Therefore, the effect size found in the present study lies within the range found in the meta-analysis. This trait was more marked in AN versus BD probands, which fits with previous literature (Harrison et al 2010b). There was a trend for difficulties in emotion recognition in non-AN cotwins with a small effect size. Moreover within pair correlations for monozygotic twins were more than double that of dizygotic twins, suggesting that there might be genetic variance in this trait. Supporting this, the literature in other conditions such as autistic spectrum disorder and schizophrenia (Losh and Piven 2007; Baron Cohen et al 1997; de Achaval et al 2009; Ibanez et al 2010) also suggest that this is a familial trait.

The attentional bias to angry faces in ED probands was with a medium effect size. Probands with BD had a greater attentional bias to angry threat stimuli in comparison to AN probands (BD: d=0.7 and AN: d=0.3). Interestingly Harrison and colleagues (2009; 2010b) found greater social attentional biases in BN (d=0.82) in comparison to AN (d=0.61), although no differences in angry threat attentional biases. Unaffected twin siblings of those with BD also had an attentional bias to angry threat stimuli at trend level suggesting that this may be a familial trait. There was support for the heritability of social attentional bias, since within pair correlations for monozygotic twins were more than double that for dizygotic twins. Similar to the findings in control samples, it may be that genetic variations in serotonin function underpin these anomalies, although molecular genetic studies in people with eating disorders would be needed to confirm this (Beevers et al 2009; Fox, Ridgewell and Ashwin 2009).

Our relatively recovered sample may account for the smaller effect sizes in comparison to previous research (Harrison et al 2010c). Previously studies have found social and angry threat attentional biases to persist in those recovered from AN in an attenuated form (Harrison et al 2010c).

Lastly, difficulties in emotion regulation (measured by the DERS) were associated with the illness and present in the unaffected twin siblings suggesting that this may be a familial risk trait. To our knowledge the familial risk of these traits in EDs has not yet been investigated. Furthermore a review paper has concluded that research investigating the genetic contributions of emotion regulation is sparse (Canli, Ferri and Duman, 2009). Nevertheless, molecular genetic studies in representative samples have lent support to the intrinsic role of the serotonin and dopamine systems in modulating emotion (Bertolino et al 2005; van Strien, 2002; van Strien, Frijters, Bergers, & Defares, 1986).

Difficulties in emotion regulation (measured by the DERS) were positively associated with increased levels of behavioural inhibition (measured by the BIS/BAS). Furthermore attentional bias to social stimuli was positively associated with the duration of bingeing. This supports the suggestion that emotional processing difficulties and increased sensitivity to threat in interpersonal situations may trigger the use of externalising strategies such as binge eating and general impulsive behaviours to regulate emotion (Aldao, Nolen-Hoeksema and Schweizer, 2010; Hartmann et al 2009).

8.8.1. Limitations

Our study has strengths of the twin design, which has been used to parse out the genetic and environmental factors that contribute to emotional processing. However, the study is constrained by low power and a heterogeneous diagnostic case mix at various stages of the illness and recovery. Another limitation is that there was insufficient resource to systematically review environmental experiences. Furthermore, we chose not to adjust for depression in our clinical sample as this is a common comorbidity of ED.

8.9. Conclusions

The findings from this study were limited for the reasons discussed above and most importantly due to the limited sample size. The findings suggest that emotional processing abnormalities vary across the diagnostic spectrum with difficulties in emotion recognition elevated in AN and angry threat attentional bias being greater in BD. There was evidence to support a familial or genetic basis to some elements of emotional processing. With this in mind future studies with larger samples and those adopting longitudinal designs should be conducted to explore whether emotional processing difficulties are truly endophenotypes that lie between the clinical

symptoms and the genes that confer risk. Such investigations may have potential implications for the future diagnosis and screening of eating disorders.

9. Chapter 9: Reward Sensitivity as an Endophenotype of Eating Disorders: a Preliminary Investigation in Twins

9.1 Introduction to the chapter

The present study builds on chapter 6, which concluded that impulsive behaviours are a familial trait in eating disorders. One hypothesis is that impulsive behaviours arise from an altered sensitivity to reward.

This chapter describes an experimental assessment of altered reward sensitivity in twins with eating disorders in an effort to gain evidence of their potential endophenotype status in terms of their familial and genetic risk as outlined by Gottesman and Gould (2003).

9.2 Background and development of the study

Sensitivity to reward varies significantly between individuals. Individuals high in reward sensitivity may experience more intense food cravings and be more likely to be overweight or develop eating disorders that involve binge eating (Beaver et al, 2006). Research into normal samples has found reward sensitivity; motivation related to behaviours and affect, which is measured by the Behavioural Inhibition System and Behavioural Activation System Scales (Carver and White, 1994) to be positively correlated with activation in the fronto-striatal amygdala-midbrain network in response to images of appetising foods such as chocolate and pizza (Beaver, et al. 2006). The fronto-striatal amygdala-midbrain network has been previously implicated as having a role in drug reward (Kelley and Berridge, 2002). The amygdala which is involved in emotional processing has been implicated in responses to monetary reward (Bechara et al 1999; Elliot et al 2003).

Eating disorders that involve binge eating often exhibit behaviours that are reminiscent of addiction and altered reward sensitivity. Disorders involving binge eating (i.e. bulimia nervosa and binge eating disorders) are characterised by a conditioned behavioural cycle that involves periods of extreme food restriction followed by binge eating highly dense calorific palatable foods (Alpers & Tuschen-Caffier, 2004) and purging. Animal models have shown that this behavioural cycle creates biological changes that encourage addictive behaviours (Rada et al 2005; Avena et al 2005; Boggiano et al 2007; Boggiano et al 2005; Avena & Hoebel 2003; Corwin 2006; Corwin & Hajnal 2005). Research in rats has shown specifically that it is the consumption of highly dense calorific palatable foods that have the greatest Pavlovian conditioning effects in comparison to low density calorific foods (Sansa et al 2009). In humans the acute state of eating disorders is associated with anomalies in neuroendocrine substances

(i.e. leptin and ghrelin) that are known to be involved in mediating appetite. These changes encourage the maintenance of eating disorder symptoms (i.e. physical hyperactivity in AN or the maintenance of binge eating in BN) (Monteleone, Castaldo and Maj, 2008).

Self report measures of sensitivity to reward such as the behavioural inhibition and activation scales (Carver and White, 1994) have demonstrated differences within the eating disorder spectrum, in that restrictive types have been found to be the least sensitive to reward and associated with higher levels of behavioural inhibition and bulimic types have been found to be the most sensitive to reward with higher levels of behavioural activation (Harrison et al 2010d; Bijttebier et al 2009). Experimental tasks that measure sensitivity to monetary reward such as the Game of Dice task (Brand et al 2005a) have also confirmed that bulimic individuals show more risky decision making in comparison to restrictive eating disorder types (anorexia nervosa and anorexia binge purge) and healthy controls (Brand et al 2007; Harrison, Macare, Cardi, Kanakam and Treasure unpublished data). People with eating disorders (AN, BN and BED) also have poor performance on the Iowa Gambling task (Bechara et al 1993; Brogan, Hevey and Pignatti, 2010; Cavedini et al 2006; Cavedini et al 2004; Tchanturia et al 2007; Boeka and Lokken 2005; Liao et al 2009; Davis et al 2010).

A study of people recovered from anorexia nervosa (Tchanturia et al 2007) have shown performance on the Iowa Gambling task (Bechara et al 1993) to be normal, suggesting that altered reward sensitivity may be related to the acute state. However, there exists substantial evidence to indicate that reward sensitivity also has a genetic component that exists beyond the acute state. Studies of normal twin samples indicate that behavioural inhibition and activation are genetically influenced traits (Takahashi, et al 2007). There is additional evidence from molecular genetic studies to suggest that these traits have a biological basis rooted in the COMT and DRD2 *Taq*1A polymorphisms which influence activity of the dopamine system (Reuter et al. 2006). In clinical AN samples, reward sensitivity has been found to be a familial risk factor (Wade et al 2008; Karwautz et al 2002) and conditions that are associated with dysregulated reward systems such as alcohol and substance use disorders have been found to co-segregate within family members of women with bulimia nervosa (Bulik, 1991; Kaye et al. 1996).

At present, the current evidence base is limited and it remains unclear as to whether altered reward sensitivity and anomalies in the associated biological processes (i.e. substances that regulate appetite such as leptin and ghrelin; Monteleone, Castaldo and Maj, 2008) precede the onset of eating disorders or are a consequence of the nutritional changes that occur during the acute state (Monteleone et al 2008). The focus of the present study was to investigate the familial and genetic risk of reward sensitivity measured by the experimental task; The Game of

Dice Task (Brand et al 2007) and self-report measures [BIS/BAS, Carver and White, 1994; appetitive motivation scale (AMS), Jackson and Smillie, 2004] in twins with eating disorders.

9.3 Aims

The aim of this study was to explore whether altered reward sensitivity might be considered as an endophenotype of eating disorders using a genetically sensitive design (a twin study). Three endophenotype criteria outlined by Gottesman & Gould (2003) were investigated. The precise aims were as follows: a) to assess the association between altered reward sensitivity and the illness by comparing eating disorder twins with controls; b) to assess co-segregation within families by comparing risky decision making, the BIS/BAS and AMS in non-eating disorder co-twins with controls; c) to examine altered reward sensitivity in relation to clinical features of the disorder in probands; d) to examine heritability by comparing within pair similarity in MZ twins against DZ twins.

9.4 Hypotheses

The main hypothesis was that people with eating disorders would demonstrate altered reward sensitivity with differences found across the eating disorder spectrum. Investigations into their twin siblings would indicate that these are familial and genetic risks factors.

In relation to the first aim, it was hypothesised that people with bulimic eating disorders would show greater risky decision on the game of dice in comparison to controls and the restricted eating disorder group. It was also predicted that people with anorexia nervosa would report higher levels of behavioural inhibition in comparison to bulimic disorders and control twins. Furthermore, people with bulimic disorders would report higher levels of behavioural activation in comparison to anorexia nervosa and controls.

In relation to the second objective, it was anticipated that non-eating disorder cotwins would show similar levels of risky decision making and behavioural inhibition and activation to their probands. Therefore, non-AN cotwins would show less risky decision making and higher levels of behavioural inhibition in comparison to control twins and non-BD cotwins. Furthermore, non-BD cotwins would show greater risky decision making and higher levels of behavioural activation in comparison to control twins and non-AN cotwins.

Finally, it was expected that altered reward sensitivity would be more similar within monozygotic twin pairs in comparison to dizygotic twin pairs, thus demonstrating a genetic basis.

9.5 Methods

9.5.1 Study design

This study employed a familial (section 3.15.5) and twin design (3.15.6) as described in detail in chapter 3.

9.5.2. Participants

Participants were the clinical and control twin groups described in chapter 3 (3.10). From this sample one concordant monozygotic twin pair was excluded since they were unable to take part in the present study. Therefore, the present sample included 25 monozygotic twin pairs and 10 dizygotic twin pairs where at least one had an eating disorder history as defined by the DSM-IV (4^{th} edition, APA, 2000). The control group included a total of 42 twins (17 monozygotic twin pairs and 4 dizygotic twin pairs).

9.6. Materials

9.6.1 Clinical assessment

The EATATE semi structured interview was administered to all probands and non-ED cotwins to determine current and lifetime eating disorder pathology and lifetime impulsive behaviours (Anderluh et al, 2003) (as described in chapter 3, section 3.5.3).

All participants also completed the BIS/BAS (behavioural inhibition system and behavioural activation system scales: Carver and White, 1994; described in chapter 8, section 8.5.5.2) as an indication of punishment sensitivity and behavioural approach respectively, the AMS (the appetitive motivation scale: Jackson and Smillie, 2004; described in chapter 8, section 8.5.5.3) as an indication of reward reactivity and the National Adult Reading Test (Nelson and Willison 1991) as an indication of premorbid IQ (described in chapter 3, section 3.4.3).

9.6.2. Behavioural assessment of altered reward sensitivity

9.6.2.1 Game of Dice Task (GDT; Brand, Fujiwara, Borsutzky, Kalbe, Kessler and Markowitsch 2005a)

The Game of Dice Task is a computerised task that is used to measure decision-making under conditions of reward and punishment. Participants are required to gamble virtual money on the result of the roll of a die (see Appendix 1.18). At the beginning participants are given explicit instructions that their goal is to win as much money as possible. They are also told of the possible consequences of each choice and that there is no time limit. The participant begins with $1000. Over 18 rounds the participant can choose a combination of fixed alternatives that

range from one number to a combination of two, three, or four numbers. The consequences of selecting risky choices (1 and 2 numbers) result in a $1000 or $500 loss or gain. The consequences of selecting safe choices (3 and 4 numbers) result in a $200 or $100 loss or gain. These consequences are made explicit to the participant at the beginning of the task.

After each choice the virtual die is rolled. If the number rolled matches a selected number or a number in their selected combination the participant will gain money. Gains are signalled by a cash machine sound and an increase in the sum of money, whereas losses are signalled by a negative noise and a decrease in the sum of money. Participants can continue to gamble even when the sum of money available is negative. The monetary balance is displayed to the participant throughout the task. The outcome variable was the number of risky choices with a higher score indicating a more risky, less safe strategy. The task is described as having good convergent validity in that it has previously shown risky decision making in patients with opiate dependence (Brand, Roth-Bauer, Driessen and Markowitsch, 2008), pathological gambling (Brand, Kalbe, Labudda, Fujiwara, Kessler and Markowitsch, 2004), ADHD (Dreschler, Rizzo and Steinhausen, 2008), binge eating disorder (Svaldi, Brand and Tuschen-Caffier, 2010) and bulimia nervosa (Brand, Frankie-Sivert, Jacoby, Markowitsch and Tuschen-Caffier, 2007).

9.6.2.2 Justification of reward sensitivity measure selection

'The Game of Dice Task' (Brand et al, 2005a) is a measure of reward sensitivity that was chosen on the basis of a pilot study as well as previous research (Brand, Frankie-Sivert, Jacoby, Markowitsch and Tuschen-Caffier, 2007). The pilot study (Harrison et al, unpublished data) assessed a total of 96 participants which included 57 people in the clinical group with AN, AN-BP or BN and 39 control participants. The participants were tested on four tasks to assess reward sensitivity and impulsivity. Three of these were from the Laboratory Behavioural Measures of Impulsivity software package (Dougherty, Mathias, Marsh and Jagar, 2005); 1) TCIP (the two choice impulsivity paradigm) and 2) SKIP (the single key impulsivity paradigm) which are reward-directed programs that assess an individual's ability to delay responding to a reward and 3) TIME (the time paradigm) that assesses an individual's ability to estimate the passage of time. The tasks assess processes involved in the ability to tolerate a delayed reward, inhibit a previously initiated response and estimate time. These processes are important in understanding impulsive behaviours (Dougherty, Mathias, Marsh and Jagar, 2005).

In addition, the pilot study (Harrison et al, unpublished data) included 'the Game of Dice Task' (Brand et al, 2005a). The results showed that 'the Game of Dice Task' (Brand et al, 2005a) was the most sensitive measure since the largest differences on outcome scores were found between clinical and control groups. In addition the task detected differences in risky decision making across the eating disorder spectrum; between anorexia nervosa and bulimia nervosa.

Previously, research has also indicated that this task detects differences in risky decision making in eating disorders that range from ANR, BN, to BED (Harrison et al unpublished data; Brand et al 2007; Svaldi, Brand and Tuschen-Caffier 2009). These studies found the highest levels of risky decision making in bulimic disorders (BN and BED). Brand and colleagues (2007) found that this measure was correlated with executive dysfunction indicating that poor performance is related to altered reward sensitivity as well as executive functioning abnormalities. 'The Game of Dice Task' is also cost free (available from the author upon request) and takes approximately 8 minutes to administer, making it a practical addition to the protocol.

9.7. Statistical methods

9.7.1. Construction of game of dice variable

The outcome variable was the game of dice risky choices. A higher score indicates riskier decision making.

9.7.2 Construction of the behavioural activation composite variable

The three behavioural activation subscales - reward, fun seeking and drive were averaged to form an overall behavioural activation composite score. The behavioural inhibition scale was analysed as a total score of its individual items.

9.7.3 Data analysis

The statistical procedures are those described in chapter 3 (section 3.15).

Previous research from our unit used the Game of Dice 'net score' (safe choices minus risky choices) as the outcome variable. In the present study this outcome variable was not normally distributed. Applying a logarithm transformation to this variable was unsuitable since this outcome measure can be a negative number. Therefore, the game of dice 'risky choices' was chosen as an outcome measure for which a logarithm transformation was applied. This outcome measure was used in all of the analysis within the present study.

9.7.4 Sample size and power

A post hoc-power analysis was conducted using GPower software due to the exploratory nature of the study. This indicated that the present sample would have 47% and 14% power for detecting group differences between BD probands and AN probands and controls at the 0.05 level for the Game of Dice respectively (based on Harrison et al unpublished data). In addition the present sample would have 95% power for the BIS, 73% power for BAS fun seeking, 25 %

for the BAS reward and 16% power for the BAS drive in detecting group differences between probands and controls at the 0.05 level (Harrison et al 2010d)

9.8. Results

9.8.1. Demographic features of clinical and control twins

The demographic and clinical features of the clinical and control group are described in chapter 3 (section 3.10).

9.8.2. Analysis of the game of dice risky decision making as associated with eating disorders and as a familial trait

Table 9.1 represents the results from the Game of Dice Task.

i) Eating disorder twins vs. control twins

Overall eating disorder probands (d=0.0, p=0.52) did not differ from controls for the number of risky choices made. Specifically, AN probands (d=0.0, p=0.79) did not differ from controls however BD probands (d=0.3, p=0.54) had a higher number of risky choices at trend level with a small effect size (d=0.3). Those who were currently underweight (n=6, raw mean=5.33, s.d=3.98) had a lower number of risky choices than those who were weight recovered (n=45, raw mean =6.76, s.d =5.06) with a small effect size (d=0.3).

ii) Non-eating disorder cotwins vs. control twins

Overall non-eating disorder cotwins (d=0.0, p=0.81) did not differ from controls for the number of risky choices made. Non-AN cotwins (d=0.3, p=0.19) had a higher number of risky choices at a minimum trend level with a small effect size whereas non-BD cotwins had less risky choices (p=0.1, d=0.5) in comparison to controls at a minimum trend level with a medium effect size.

Table 9.1: Analysis of the Game of Dice Risky Choices as Associated with Eating Disorders and as a Familial Trait

Analysis of the Game of Dice for 'Overall Groups': Probands, Non-ED Cotwins and Controls

Game of Dice (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**		
Game of dice risky choices[1]	6.6 (4.9)	5.3 (4.5)	5.9 (4.9)	Wald Chi Square: 0.46, df: 2. p= 0.79	
				Proband = Controls, 0.05 (-0.11-0.21) p=0.52	(d=0)
				Non ED cotwin = Controls, 0.02 (-0.16-0.21) p=0.81	(d=0)
				Probands = Non ED cotwins, 0.03 (-0.13-0.19) p=0.70	(d=0)

Analysis of the Game of Dice for 'Overall Groups' Sub-Divided by Eating Disorder Diagnosis

Game of Dice (Raw Scores)						Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
Specific Diagnosis (NB)	**AN (n=24)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**		
Game of dice risky choices[1]	6.2 (4.8)	6.7 (5.2)	6.1 (4.7)	2.7 (2.9)	5.9 (4.9)	Wald Chi Square: 7.33, df: 4. p= 0.13	
						AN = Controls, -0.03 (-0.17-0.22) p=0.79	(d=0)
						BD > Controls, -0.05 (-0.12-0.23) p= 0.54	(d=0.3)
						Non-AN cotwin >. Controls, 0.13 (-0.06-0.32) p=0.19	(d=0.3)
						Non-BD cotwin < Controls, -0.22 (-0.49-0.04) p= 0.1	(d=-0.5)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
Controls twins: Monozygotic and dizygotic twins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the Game of Dice (risky choices) were analysed after a logarithm transformation and age included as a covariate.
* = P<0.05
** = P<0.01

9.8.3. Analysis of the AMS as associated with eating disorders and as a familial trait

Table 9.2 represents the results from the AMS.

i) Eating disorder twins vs. control twins

Overall eating disorder probands had a lower AMS score in comparison to controls at trend level with a medium effect size (d=0.4, p=0.06). Both AN probands (d=0.5, p=0.12) and BD probands (d=0.4, p=0.16) similarly had a lower AMS score in comparison to controls at trend level with a medium effect size. Those who were currently underweight (n=6, raw mean=26.4, s.d=8.29) had a lower AMS score in comparison to those who were weight recovered (n=45, raw mean =30.50, s.d =9.25) with a medium effect size (d=0.46).

ii) Non-eating disorder cotwins vs. control twins

Overall non-eating disorder cotwins (d=0.08, p=0.82) did not differ from controls for their AMS score. Non-AN cotwins did not differ from controls for their AMS score (d=0.0, p=1.0) although Non-BD cotwins had a lower AMS score at trend level with a small effect size (d=0.24, p=0.72).

Table 9.2: Analysis of the AMS as Associated with Eating Disorders and as a Familial Trait

Analysis of the AMS for 'Overall Groups': Probands, Non-ED cotwins and Controls

AMS (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins n=42)**		
AMS total[1]	30.1 (6.7)	30.4 (8.1)	31.8 (4.4)	Chi Wald Square=3.78, df=2, p=0.15	
				Proband < Controls, -2.20 (-4.47-0.07) p=0.06	(d=0.4)
				Non-ED cotwin < Controls, -0.45 (-4.32- 3.41) p=0.82	(d=0.08)

Analysis of the AMS for 'Overall Groups' Sub-Divided by Eating disorder Diagnosis

AMS (Raw Scores)						Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
Specific Diagnosis (NB)	**AN (n=24)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**		
AMS total[1]	29.5 (7.1)	29.6 (6.3)	31.2 (9.9)	29.3 (5.2)	31.8 (4.4)	Chi Wald Square=4.94, df=4, p=0.29	
						AN < Controls -2.45 (-5.57-0.67) p=0.12	(d=0.5)
						BD < Controls -1.97 (-4.69- 0.75) p=0.16	(d=0.4)
						Non-AN cotwins = Controls -0.01 (-5.42-5.40) p=1.0	(d=0.0)
						Non-BD cotwins <Controls -1.06 (-6.89-4.78) p=0.7	(d=0.24)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
Controls twins: Monozygotic and dizygotic twins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the AMS included age as a covariate
**= P <0.01
*= P <0.05

9.8.4. Analysis of the BIS/BAS as associated with eating disorders and as a familial trait

Table 9.3 represents the results from the BIS/BAS.

i) Eating disorder twins vs. control twins

Overall eating disorder probands had a significantly higher BIS score in comparison to controls with a medium effect size (d=0.53, p=0.01). Both AN probands (d=0.5, p=0.03) and BD probands (d=0.61, p=0.16) similarly had a higher BIS score in comparison to controls at trend level with a medium effect size. Those who were currently underweight (n=6, raw mean=26.17, s.d=2.04) had a higher BIS score in comparison to those who were weight recovered (n=45, raw mean =22.20, s.d =3.41) with a large effect size (d=1.23).

Eating disorder probands had a significantly lower BAS score in comparison to controls with a medium effect size (d=0.5, p=0.01). Both AN probands (d=0.6, p=0.03) and BD probands (d=0.6, p=0.05) had a significantly lower BAS score in comparison to controls. Those who were currently underweight (n=6, raw mean=9.61, s.d=3.14) had a lower BAS score in comparison to those who were weight recovered (n=45, raw mean =12.55, s.d =2.30) with a large effect size (d=1.26).

ii) Non-eating disorder cotwins vs. control twins

Overall non-eating disorder cotwins had a higher BIS score in comparison to controls at trend level with a medium effect size (d=0.4, p=0.51). Non-AN cotwins did not differ from controls for their BIS score (d=0.13, p=0.76) although non-BD cotwins had a significantly higher BIS score in comparison to controls with a large effect size (d=1.2, p=0.0).

Non-eating disorder cotwins had a lower BAS score in comparison to controls (d=0.4, p=0.19) at trend level. Non-AN cotwins (d=0.2, p=0.5) had a lower BAS score in comparison to controls at trend level with a small effect size whereas non-BD cotwins (d=0.9, p=0.05) had a significantly lower BAS score in comparison to controls with a large effect size.

Table 9.3: Analysis of the BIS/BAS as Associated with Eating Disorders and as a Familial Trait

Analysis of BIS/BAS for 'Overall Groups': Probands, Non-ED cotwins and Controls

BIS/BAS (Raw Scores)				Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
	Probands (n=51)	**Non-ED cotwins (n=19)**	**Control twins (n=42)**		
BIS[1]	22.7 (3.5)	22.2 (3.7)	21.0 (2.7)	Chi Wald Square=6.09, df=2, p=0.05	
				Proband > Controls, 1.66 (0.34-2.97) p=0.01	(d=0.53)
				Non ED cotwin > Controls, 1.14 (-0.67-2.94) p=0.51	(d=0.4)
BAS[1]	12.2 (2.6)	12.2 (2.6)	13.3 (1.8)	Chi Wald Square=6.7, df=2, p=0.04	
				Proband < Controls, -1.12 (-2.14- -0.28) p=0.01	(d=-0.5)
				Non ED cotwin < Controls, -0.87 (-2.18-0.43) p=0.19	(d=-0.43)

Analysis of the BIS/BAS for 'overall groups' Sub-Divided by Eating Disorder Diagnosis

BIS/BAS (Raw Scores)						Group comparisons, ***Mean difference (95% C.I) p value***	Cohen's *d*
Specific Diagnosis (NB)	**AN (n=24)**	**BD (n=26)**	**Non-AN cotwins (n=12)**	**Non-BD cotwins (n=6)**	**Control twins (n=42)**		
BIS[1]	23.2 (2.7)	22.2 (4.2)	21.3 (3.9)	24.32 (2.7)	21.0 (2.7)	Chi Wald Square=14.33, df=4, p=0.01	
						AN > Controls 1.63 (0.17-3.09) p=0.03	(d=0.5)
						BD > Controls 1.62 (-0.29-3.53) p=0.1	(d=0.61)
						Non-AN cotwins = Controls 0.35 (-1.89-2.60) p=0.76	(d=0.13)
						Non-BD cotwins > Controls 3.15 (1.27-5.03) p=0.0	(d=1.2)
BAS[1]	11.9 (2.8)	12.4 (2.5)	12.5 (3.1)	11.4 (1.3)	13.3 (1.8)	Chi Wald Square=10.08, df=4, p=0.04	
						AN < Controls -1.31 (-2.50- -0.11) p=0.03	(d=0.6)
						BD < Controls -1.05 (-2.13-0.02) p=0.05	(d=0.6)
						Non-AN cotwins < Controls -0.64 (-2.50-1.20) p=0.50	(d=0.2)
						Non-BD cotwins < Controls -1.50 (-2.13-0.02) p=0.05	(d=0.9)

NB: monozygotic twin pair whose proband had a diagnosis of EDNOS inappropriate compensatory behaviours was excluded from this analysis.
Proband: Monozygotic probands, dizygotic probands
Non-ED cotwin: Monozygotic and dizygotic non-eating disorder cotwins
AN: Anorexia nervosa (Anorexia binge purge type and EDNOS AN)
BD: Bulimic disorders (BN, EDNOS BN and BED)
Non-AN cotwin: Monozygotic and dizygotic non-anorexia nervosa cotwins
Non-BD cotwin: Monozygotic and dizygotic non-bulimic disorder cotwins
Controls twins: Monozygotic and dizygotic twins
Descriptive statistics presented are raw means and standard deviation (1 d.p)
[1] Data analysis about the BIS/BAS were analysed with age included as a covariate

9.8.5. Relationship between the game of dice, AMS, behavioural inhibition and activation and clinical features

In probands, non-ED cotwins or controls the game of dice risky choices was not significantly associated with any eating disorder symptoms, lifetime impulsive behaviours or behavioural inhibition and activation scores.

In eating disorder probands a higher BAS composite score was associated a lower duration of dieting, (r=-0.34, p=0.00) fasting (in months) (r=-0.31, p=0.00) and use of inappropriate compensatory behaviours (r=-0.30, p=0.00).

9.8. 6. Relationship between the game of dice, AMS, behavioural inhibition and activation

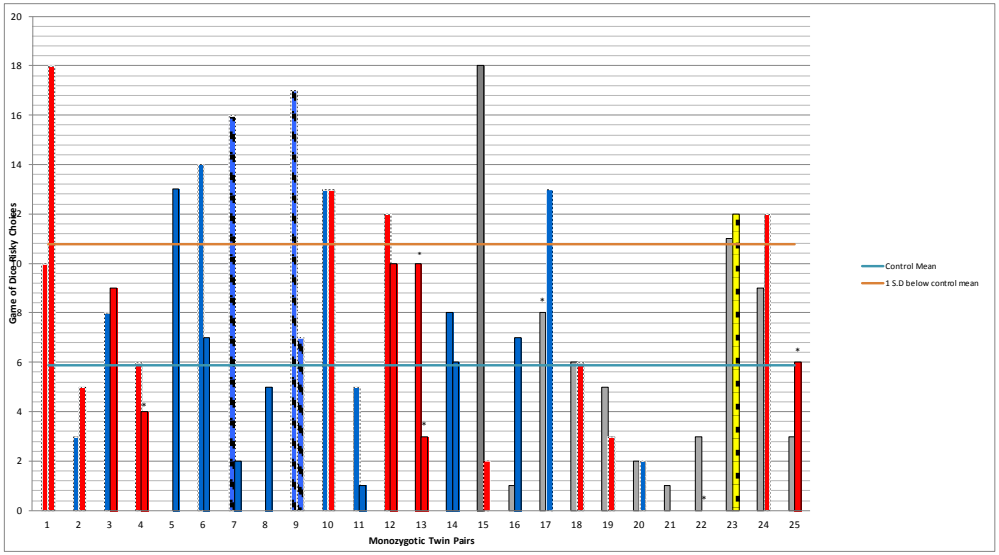
A higher AMS total score was associated with a higher BAS composite score in probands (r=0.74, p=0.00), non-ED cotwins (r=0.78, p=0.00) and controls (r=0.54, p=0.00).

9.8.7 Analysis of the game of dice risky choices as heritable

Legend

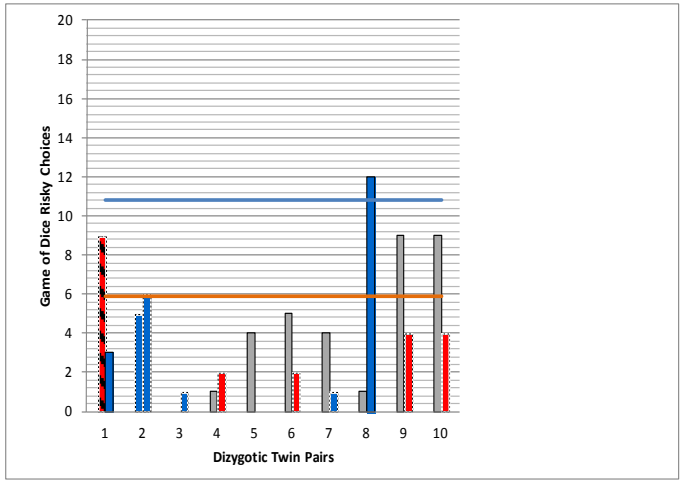
Diagram 9.1: Game of Dice Risky Choices in MZ and DZ Twins

Diagram 9.1a: Game of Dice in MZ Twins Pairs



Y axis: Game of dice net score (raw score)
X axis: Twin pair (Twin pairs 1 to 14 are concordant for ED diagnosis. Twin pairs 15 to 24 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control twin mean

Diagram 9.1b: Game of Dice in DZ Twins Pairs



Y axis: Game of dice net score (raw score)
X axis: Twin pair (Twin pairs 1 to 2 are concordant for ED diagnosis. Twin pairs 2 to 10 are discordant with twin 2 indicating the proband)
1 S.D below control mean- 1 standard deviation below control twin mean

9.8. 7.1. Summary of game of dice risky decision making as a heritable trait

An inspection of monozygotic twins in diagram 9.1a shows twin pairs concordant for eating disorders are relatively discordant in their game of dice performance in comparison to those who are discordant for eating disorders. For reward sensitivity measured by the Game of Dice task, the within pair correlation for monozygotic twins [r=0.20, (CI:-0.21 – 0.54), p=0.17] was only marginally greater than that for dizygotic twins [r=0.07 (CI: -0.65 – 56) p=0.58]. Neither of these within pair correlations reached statistical significance.

9.8.8. Analysis of behavioural inhibition and activation scale and AMS as heritable

Table 9.4: Analysis of the BIS/BAS and AMS as Heritable Traits

	Monozygotic twins	*Dizygotic twins*
BIS	0.29 (-0.13-0.62) p=0.08	0.52 (-0.16-0.87) p=0.06
BAS	0.65 (0.33-0.83) p=0.00*	-0.12 (-0.69-0.56) p=0.62
AMS	0.65 (0.34 -0.84) p=0.00*	-0.74 (-0.93- -0.20) p=0.99

Intraclass correlation coefficients with confidence intervals in brackets
BIS: Behavioural inhibition scale (Carver and White, 1994)
BAS: Behavioural activation composite score (Carver and White, 1994)
AMS: Appetitive motivation scale (Jackson and Smillie, 2004)
* =P<0.05

9.9. Discussion

The aim of the present study was to investigate whether altered reward sensitivity was associated with eating disorders, a familial and heritable trait. The traits were investigated using three different measures; a computerised Game of Dice Task (Brand et al 2005a), the self-report BIS/BAS (punishment sensitivity and behavioural approach; Carver and White, 1994) and the AMS (reward reactivity; Jackson and Smillie, 2004). Risky decision making measured by the Game of Dice Task was elevated in BD probands at trend level. However this was not predictive of specific clinical features in probands nor was it found in unaffected twin siblings or to be largely heritable. Similar to previous findings (Harrison et al 2010d; Bijttebier et al 2009), the behavioural inhibition and activation systems were found to be associated with eating disorders, and the findings suggested that they were also a familial and genetic risk. The evidence from this study indicates that each measure of reward sensitivity assesses different facets of its component, since each has different levels of genetic basis and are not necessarily correlated with each other. The Game of Dice task appears to have less diagnostic use in this relatively recovered sample, in comparison to the BIS/BAS which appears to measure stable features associated with lifetime eating disorders.

9.9.1 Game of dice risky choices as endophenotypes of eating disorders

In line with our hypothesis, risky decision making was found in bulimic disorders at trend level with a small effect size (d=0.3). In comparison to previous research which has found much larger effect sizes for risky decision making in BDs (bulimia nervosa and binge eating disorder) (Harrison et al unpublished data; Svaldi Brand and Tuschen-Caffier 2009; Brand et al 2007) the present study's sample was more than two thirds (63%) in a recovered state. Previous research has shown disadvantageous decision making measured by the Iowa Gambling task (Bechara et al 1997) to return to normal in those recovered from AN (Tchanturia et al, 2007). In line with this, probands in the present study who were currently underweight made fewer risky choices in comparison to those with a normal BMI (small effect size). Although the particularly small sample size for this comparison is a limitation, this notable finding does require further discussion. Previous research has demonstrated that the acute state of eating disorders involves anomalies in the levels of neuroendocrine substances, which are involved in the modulation of food intake. These include adipokines leptin, adiponectin and resistin, the gut-related peptides' ghrelin and peptide YY (PYY), the neurotrophin brain-derived neurotrophic factor (BDNF) and endocannabinoid substances (Monteleone, Castaldo and Maj, 2008). These changes can moderate the symptoms of eating disorders and levels of reward sensitivity. For example, in the acute state of AN there is decreased levels of leptin (Grinspoon et al 1996) and increased levels of ghrelin (Otto et al 2001) which may mediate the maintenance of amenorrhea and physical hyperactivity in emaciated patients (Monteleone, Castaldo and Maj, 2008). In

eating disorders, that involve episodes of binge-purge cycles with vomiting there may be hyposecretion of leptin (Monteleone et al 2002) and increased levels of ghrelin (Tanaka et al 2003). These biological changes may further moderate the maintenance of binge eating behaviours in the acute state (Monetelone et al 2008). Therefore it may be proposed that reward sensitivity assessed by the Game of Dice task (Brand et al 2008) is more sensitive to an underweight status or current eating pathology, especially eating behaviours involving fasting or purging which are known to produce biological changes (Rada et al 2005; Avena et al 2005; Boggiano et al 2007; Boggiano et al 2005; Avena & Hoebel 2003; Corwin 2006; Corwin & Hajnal 2005). These post onset factors may account for the large differences in the game of dice performance within some monozygotic twin pairs.

The following hypothesis which proposed altered reward sensitivity (measured by the Game of Dice task) to be a familial risk was not supported. Previous research has shown that adolescents with ADHD make significantly more risky choices on the Game of Dice task (Dreschler, Rizzo, and Steinhausen, 2008). The familial risk of Game of Dice task performance is yet to be investigated however other research has found intermediate performance in unaffected siblings of those with ADHD on another task measuring aspects of impulsivity and altered reward sensitivity: the Go/Nogo-Task (Uebel et al 2010). This suggests that traits measured by the Go/Nogo-Task such as the ability to inhibit a previous response and related processes such as motivation and sustained attention are familial traits (Uebel et al 2010). To explain the discrepancy in this being a familial trait in ADHD (Uebel et al 2010) but not in eating disorders it should be acknowledged that a number of processes are thought to underlie impulsive behaviour, including behavioural inhibition, attention, working memory, emotion and the value of reinforcement over time (Acre and Santisteban, 2006). There may subtle be differences between the Go/Nogo-Task and Game of Dice task in the processes required for performance. The Go/Nogo-Task measures the ability to inhibit a previously initiated response whereas the Game of Dice task measures decision making under conditions of reward and punishment (Brand et al 2008).

In respect of the last hypothesis, performance on the game of dice task showed a trend towards heritability with monozygotic twins being more similar in performance in comparison to dizygotic twins. Although it is noted that neither of these within pair correlations reached statistical significance.

9.9.2 Behavioural inhibition and activation system as endophenotypes of eating disorders

The hypothesis which proposed significant differences in behavioural inhibition and activation between AN and BD probands was not confirmed. However, behavioural inhibition was more strongly associated with the duration of restrictive ED behaviours. For the behavioural activation

composite score, a higher score was positively associated with a lower duration of fasting, dieting and use of inappropriate compensatory behaviours. This may lend support to the increased use of dimensional behaviours such as the duration of individual clinical symptoms (as opposed to using diagnostic categories which are based on attaining a minimum count) to assess clinical severity (Mazzeo et al 2009).

The present study found the AMS, behavioural inhibition and activation to be heritable and familial traits in a clinical sample of twins with eating disorders. In normal samples genetic factors appear to account for approximately one third of the variance in the BIS (34%) and BAS traits (35%) (Japanese sample, aged: 25.5 yrs). In this longitudinal study (3 years) genetic factors were stable over time, however environmental factors (i.e. negative life events, peer group experiences and social support) were found to contribute to individual differences in the change of these traits over time. It was proposed that the quality of environment is dynamic and varies between individuals (Takahashi, et al 2007). Molecular genetic studies have also supported the biological basis to the BIS/BAS systems. The interaction of two polymorphisms; COMT and DRD2 *Taq*1A (which are known to influence activity of the dopamine system) significantly predicts differences in the total BAS scale. Specifically it is the disequilibrium between the catabolic enzyme activity of COMT and D2 catabolic receptor density that is associated with a higher dopamine activity and higher BAS scores (Reuter et al. 2006). Reuter et al (2006) suggested that this gene-gene interaction may explain differences in heritability estimates.

Taken together the findings of behavioural inhibition and activation being associated with ED symptoms in the clinical group and these being familial and heritable traits, it may be proposed that the dysregulation of these brain systems are endophenotypes that have specific significance for the development of eating disorders.

9.10. Conclusions

The present study set out to explore whether aspects of altered reward sensitivity that is associated with eating disorders could be considered as endophenotypes by exploring whether it was associated with the illness and a familial and heritable trait. Preliminary evidence was found to support behavioural inhibition and activation being endophenotypes of eating disorders. Conversely, in this largely recovered sample, there was less evidence to support risky decision making measured by the game of dice as an endophenotype in eating disorders.

10. Chapter 10: General Discussion

10.1 Introduction to the chapter

This chapter discusses the findings of this thesis. The overall objective of this research was to understand whether anomalies in cognitive, emotional and behavioural functioning in people with eating disorders could be genetically determined traits that increase the risk of developing the illness.

At present, eating disorders are diagnosed and treated on the basis of their visible symptoms. The wide heterogeneity within each diagnostic category and frequent fluctuation in symptoms over time can make this diagnostic process difficult (Treasure, Claudino and Zucker, 2010; Eddy et al 2008; Mazzeo et al 2009) (see chapter 1, section 1.8 for further details). In response, proposals have been put forward for the forthcoming DSM-V which is due in 2013. These include more lenient criteria for being classed as underweight in AN and a lower frequency of binge eating (once a week) that reaches clinical significance (see chapter 1, section 1.9). The transdiagnostic conceptualisation of EDs (the grouping of all EDs into one category) is a more radical proposal (Fairburn et al 2003). This is suggested on the premise that core symptoms such as an over evaluation of weight and shape are present in all ED's (Fairburn, Cooper and Shafran, 2003; see chapter 1, section 1.9.1). The diagnosis of eating disorders is made more complex by high levels of psychiatric comorbidity, especially anxiety disorders and depression in all EDs (Godart et al 2007; Kaye et al 2004) OCD (Lavender et al., 2006) and ASD features in AN (Gillberg, Rastam and Gillberg 1996). The chronology of these disorders has further implications (Godart et al 2000). Anxiety disorders or OCD often predate the onset of EDs, suggesting that that the development of ED related behaviours are secondary to general anxiety and may assist in reducing it. The opposite may also occur whereby EDs predate the onset of anxiety disorders (Godard et al 2000). This comorbidity may be rooted at the biological level in anomalies of the serotonin system (Brewerton, 1995).

Another dimension that is important to the diagnosis of AN is its stage of severity. A concept proposed by Touyz (2012) is to diagnose the illness in stages as is done in the field of cancer. People with AN who clearly have the condition but do not meet the full diagnostic criteria (i.e. normal weight) should be diagnosed as 'stage one' whereas those with a full blown diagnosis and a high medical risk could be classed as 'stage five'.

With other medical health conditions, a gold standard to increase the efficacy of diagnosis has been to define its aetiology. Aetiological diagnosis is less advanced in the field of psychiatry, however research is underway and there is an interest in defining genetic risk factors. Genetic

studies have yet to find a specific gene that confers risk to eating disorders (see section 10.6.2). The search for risk genotypes is difficult because of their small effect sizes (Risch and Merikangas, 2006), rarity or the involvement of gene-environment or gene-gene interaction. In addition, any one genotype can be associated with a number of phenotypes (Gotttesman and Gould, 2003). It has been hypothesised that endophenotypes may have a simpler and more direct association with the genetic underpinnings of ED's. Further research is still needed to explore their association with the illness and genetic risk before these can be systematically used in the screening and diagnostic process. There have been various uses for genetic screening in the field of physical health conditions that could potentially have use in the field of psychiatry. Types of genetic screening include 1) diagnostic testing – to confirm a diagnosis and inform treatment choices, 2) Predictive and presymptomatic testing: to identify the risk of developing a condition (i.e. cancer) 3) newborn screening – to identify genetic disorders that can be treated earlier (i.e. screening for phenylketonuria) and 4) pharmacogenomics – to determine drug response.

The foremost aim of this thesis was to use twin methodology to explore endophenotype criteria of developmental phenotypes, neuropsychological and behavioural profiles. This research involved two parts. The first part involved a large sample of twins that were representative of the general population (n=3338) and were recruited from the UK twin registry (Study 1, Chapter 2). This large sample allowed for the calculation of genetic influences on self reported psychological symptoms and behaviours associated with eating disorders; body dissatisfaction, drive for thinness and bulimia. The second part of the research (Studies 2 to 7) involved a selection of twins with clinical eating disorders (n=53 met lifetime DSM-IV eating disorder criteria, n=19 non-eating disorder cotwins). This clinical sample allowed for an in-depth examination of the genetic basis to neuropsychological and behavioural traits in eating disorders. Specifically study 2 (Chapter 4) explored the evolution of clinical symptoms over time and how these co-aggregate within twin pairs. Studies 3 to 7 (Chapters 5 to 9) investigated the familial risk and genetic basis of 1) childhood obsessive compulsive personality traits (study 3, chapter 5), 2) lifetime impulsive behaviours (study 4, chapter 6), 3) neurocognitive traits such as difficulties in set shifting and weak central coherence (study 5, chapter 7), 4) emotional processing styles such as emotion recognition and social affective attentional biases (study 6, chapter 7) and lastly 8) altered reward sensitivity (study 7, chapter 8). Previously these traits have been investigated in people with eating disorders, those recovered from the illness and unaffected sibling pairs. This has allowed for all the endophenotype criteria (see chapter 1, section 1.3) to be investigated, except that of heritability which was the primary objective of this thesis. Specifically three endophenotype criteria were assessed: 1) the traits association with the illness, 2) the traits presence in unaffected twin siblings and 3) the heritability of the trait in people with eating disorders.

The following section presents the main findings. This is followed by the studies general limitations, how the findings may inform the diagnosis and treatment of eating disorders and directions for future research.

10.2 Overview of the main findings of the thesis

10.2.1. Study 1

Aims: The first study (Chapter 2) set out to explore the genetic and environmental contributions to psychological and behavioural traits associated with eating disorders. This study employed a large sample of representative twins recruited from the UK twin registry (n=3338, MZ pairs=949, DZ pairs=720). The sample completed self-report questionnaires measuring: 1) drive for thinness, 2) body dissatisfaction and 3) bulimia (measured by the EDI-2 Garner, 1991).

Findings: Structural equation modelling techniques indicated a substantial genetic basis for drive for thinness (60% of the variance accounted for by genetic factors), body dissatisfaction (genetic factors: 67%) and bulimia (genetic factors: 52%).

Implications: The similarity in levels of genetic influence on drive for thinness and body dissatisfaction may have been due to the symptomatic overlap between these symptoms. Drive for thinness is a dimensional symptom that is seen across all eating disorders and involves an amalgamation of body dissatisfaction, weight concern and dieting (Bulik et al 2007). The relatively greater influence of environmental factors (48%) on bulimia may be attributed to the recent surge in highly palatable foods and the loss of meal structure, which may encourage overeating. This representative sample of UK twins demonstrated a substantially higher genetic influence (52%) to bulimia than the only other study of this trait in a Swedish cohort (16% heritability) (Baker et al 2009). It may be that the Swedish and UK twin cohort differ in their exposure to environmental influences. These may include lifestyle and exposure to palatable foods which could have epigenetic influences on the measure of bulimia. There may also be different genetic factors between the samples (i.e. ‘binge prone’ and ‘binge resistant ’; Boggiano et al 2007). Supporting this, these cultures have different prevalence’s for obesity (in 2005, 10.7% in Sweden and 23% in the UK; Organisation for Economic Cooperation and Development).

10.2.2. Studies 2 to 7

The remaining studies of this thesis (studies 2 to 7) investigated a smaller clinical sample of twins with eating disorders (n=53 met lifetime DSM-IV eating disorder criteria, n=19 non-eating disorder cotwins). These twins were recruited for the most part from the UK twin registry and

also from a previous research study conducted by Holland, Sicotte and Treasure (1988). These studies aimed to assess the association with the illness and familial risk of neuropsychological and behavioural traits by comparing probands and unaffected twin siblings with control twins (see chapter 3, section 3.15.5). The genetic basis of these traits was assessed by comparing within pair correlations for monozygotic twins with dizygotic twins. It was expected that these would be higher in MZ twins due to them sharing 100% of genes (see chapter 3, 3.15.6.).

10.2.3. Study 2

Aims: The second study (chapter 4) sought to describe the clinical evolution of eating disorder symptoms and behaviours (assessed by the EATATE lifetime diagnostic interview; Anderluh et al 2003) and how these co-aggregate within twin pairs, beginning with birth until present day.

Findings: The evolution of symptoms over time demonstrated a greater similarity within identical twin pairs. This suggests that inherited factors contribute to the maintenance and duration of behaviours and the long term outcome of eating disorders.

Implications: At present eating disorder diagnosis is mainly based on attaining specific frequencies and durations of clinical symptoms to reach a clinical threshold. The diagnosis of AN is based on attaining a clinical threshold of a BMI below 18.5, along with a number of other symptoms for a minimum duration of 3 months. This is also the case for BN, where a diagnosis requires binge eating to occur twice a week for a minimum duration of 3 months. However the temporal element (i.e. duration of symptoms) has been neglected by the current diagnostic process. The duration of illness and persistence of clinical symptoms over time may vary between individuals. This temporal variance in symptoms may be accounted for by various genetic factors that differentially relate to the underlying phenotype (Mazzeo et al 2010).

10.2.4. Study 3

Aims: The third study (chapter 5) examined OCP traits in childhood as developmental endophenotypes associated with eating disorders. Childhood OCP traits were assessed using a semi-structured interview (EATATE lifetime diagnostic interview, Part II; Anderluh et al 2003).

Findings: Childhood OCP traits were found at a higher rate in those with an ED history (d=2.08) in comparison to controls. There were no differences in OCP traits between AN and BD probands.

OCP traits were also a familial risk since they were elevated in their unaffected twin siblings (d=1.35). Monozygotic twins [r=0.55 (CI: 0.21-0.77) p=0.00] did not demonstrate greater within

pair similarity in comparison to dizygotic twins [r=0.74 (CI: 0.25-0.93) p=0.01] suggesting that shared environmental factors may contribute more strongly to these traits.

Implications: The present findings suggest that OCP features could be used as transdiagnostic criteria for eating disorders. Since these traits were found to be a premorbid familial trait, it supports the Cognitive-Interpersonal Maintenance Model of AN (Schmidt and Treasure, 2006) which proposes perfectionism to be a risk factor for AN. OCP features appeared to be more environmentally influenced (i.e. parenting styles or peer group experiences). In contrast a large sample of representative twins have demonstrated a substantial genetic influence of 81% for childhood OCP traits (measured by the childhood retrospective perfectionism questionnaire; Southgate et al 2008) (Boraska, et al to be submitted). The difference between our clinical twins and the representative sample may be due to Bosaka's use of a self report questionnaire to probe for OCP traits as opposed to an interview. It may also be that the underlying phenotypes or rather, the etiological architecture of an OCP may differ between psychiatric and control populations (Gottesman and Gould, 2003). To confirm this proposal, research into larger samples of twins with eating disorders is required to estimate the genetic and environmental contributions.

10.2.5. Study 4

Aims: The fourth study (chapter 6) examined whether lifetime impulsive behaviours (assessed by the EATATE-Part II; Anderluh et al 2003) could be an endophenotype of eating disorders.

Findings: Overall impulsive behaviours were found at a higher rate in those with an ED history in comparison to controls. There were diagnostic differences, with a higher rate found in those with BD (d=3.25) in comparison to AN (d=1.81). In the present study, impulsive behaviours were found to be a familial risk factor (non-AN cotwins d=2.64, non-BD cotwin d=2.92). There was less evidence to support their substantial heritability (see chapter 6, section 6.6.4.1) which suggests that shared environmental factors may contribute more to their risk.

Implications: The finding of a higher rate of impulsive behaviours in BD probands supports previous work (Fernandez-Aranda et al 2009; Matsunaga et al 1998; Boisseau et al 2009; Claes et al 2001). Taken together with these being a familial trait, the findings indicate that these behaviours may be useful additions to the diagnostic assessment.

10.2.6. Study 5

Aims: The fifth study (chapter 7) explored the genetic basis of the neurocognitive traits, set shifting [assessed by the WCST (Heaton et al 1993) and the Brixton task (Burgess and

Shallice)] and central coherence [assessed by the GEFT (Witkin et al 2002) and the ROCF task (Osterrieth, 1977)] in twins with eating disorders.

Findings: Set shifting difficulties were more marked in people with eating disorders (WCST d=0.4, Brixton task d=0.2). There were no substantial differences between AN and BD probands. There was evidence to support a strength in local processing (measured by the GEFT) in AN (d=-0.3). Set shifting difficulties (WCST d=0.4, Brixton task d=0.2) and weak central coherence (measured by the ROCF task d=-0.6) were found to be familial risks. There appeared to be a genetic contribution to both neurocognitive traits (chapter 7, section 7.6.3.1 and 7.6.3.2) although this was greater for performance on the central coherence tasks (chapter 7, section 7.6.3.2).

Implications: The present work indicated that set shifting difficulties may be a useful transdiagnostic endophenotype and have uses in predicting the risk of eating disorder development. It may be particularly useful in detecting the acute state of eating disorders since difficulties were pronounced in those currently underweight as in previous research (Tenconi et al 2010; Nakazato et al 2008; Nakazato et al 2008; Tchanturia et al 2011a). In regard to weak central coherence, the present findings taken together with previous work (Lopez et al 2008a; Roberts et al 2010) indicates that this trait may be a useful diagnostic endophenotype of restrictive eating disorders.

10.2.7. Study 6

Aims: The sixth study (chapter 8) explored emotional processing styles as endophenotypes of eating disorders.

Findings: Emotion recognition (AN, d=-0.3) (measured by the reading the mind in the eyes task; Baron-Cohen et al 2003), attentional biases to social (d=0.2) and threat stimuli (d=0.5) (measured by the Estroop: Ashwin et al 2006) and difficulties in emotion regulation (d=1.1) (measured by the difficulties in emotion regulation scale; Gratz and Roemer, 2004) were associated with EDs at a minimum trend level. Angry attentional biases (non-BD cotwins d=0.6) and difficulties in emotion regulation (non-ED cotwins d=0.6) were found in their unaffected twin siblings at trend level, suggesting that they co-segregate within families. Furthermore, emotion recognition and social emotional attentional biases appeared to be substantially heritable (chapter 8, section 8.7.3.1 and 8.7.3.2).

Implications: These findings are in line with previous research (Russell et al 2009; Harrison et al 2009; Harrison et al 2010b; Harrison et al 2010c). It also lends some support to 'The Cognitive Interpersonal Model of AN' (Schmidt and Treasure, 2006) which proposes that emotional

processing difficulties are a risk factor to the development of AN. The relatively small effect sizes may be attributed to the wide variability in emotional processing profiles within eating disorders. Previous research (Harrison, 2010) has only found 11% of people with eating disorders to score in the extreme range (90th percentile of control participant data) for difficulties in social emotional processing (measured by the RME and Estroop) (Harrison, 2010). For these reasons, emotional processing measures (RME and Estroop) may be a useful addition to the diagnostic assessment in order to identify this subgroup with significant difficulties.

10.2.8. Study 7

Aims: The last study (chapter 9) investigated altered reward sensitivity (measured by the Game of Dice, Brand et al 2005a) and the behavioural inhibition and activation systems (behavioural inhibition system and behavioural activation system scales; Carver and White, 1994) as endophenotypes of eating disorders.

Findings: Bulimic disorders (effect size= 0.3) made more risky choices on the Game of Dice task (Brand et al 2005a) in comparison to controls at trend level. Whereas restrictive eating disorders performed no differently to controls (d=0). Safer decision making appeared to be amplified in the acute state of AN (i.e. currently underweight, d=0.3). There was limited evidence to support risky decision making being a familial (non-AN cotwins, d=0.3 and non-BD cotwins d=-0.5) or largely heritable trait [monozygotic twins [r=0.20, (CI:-0.21 – 0.54), p=0.17] and dizygotic twins [r=0.07 (CI: -0.65 – 56) p=0.58].

Elevated levels of behavioural inhibition (d=0.53) and reduced levels of behavioural activation (d=0.5) were associated with eating disorders. There was also evidence of higher levels of behavioural activation (BIS/BAS scales; Carver and White, 1994) being associated with a lower duration of restrictive behaviours (i.e. dieting, fasting and inappropriate compensatory behaviours). Behavioural inhibition (d=0.43) and activation (d=0.4) were familial risks (BIS: d=0.4, BAS d=0.43) and demonstrated a genetic basis (chapter 9, table 9.8.8).

Implications: These findings support Treasure's (in progress) 'Theoretical Model of Eating Disorders' which proposes that altered reward sensitivity has prognostic relevance for the development of binge eating (Favarro et al 2005; Tozzi et al 2005) since it was elevated in probands with BDs. The findings in this relatively recovered sample contrasts with previous research which has found much larger effect sizes for risky decision-making in those with current bulimic disorders (Harrison and colleagues, unpublished data; Brand et al 2007; Svaldi, Brand and Tuschen-Caffier, 2009). It was proposed that the acute state may heighten diagnostic differences in risky decision making, especially since safer decision making was highest in those who were currently underweight.

The findings that the BIS/BAS systems were a familial and genetic risk supports the hypothesis that these may be biologically based brain systems (Carver and White, 1994). Furthermore, evidence from genetic studies has shown that these traits are associated with genes (COMT and DRD2 *Taq*1A polymorphisms) that influence activity of the dopamine system (Reuter et al, 2006). In conclusion the behavioural inhibition and activation systems may be useful in determining diagnostic differences (Harrison et al 2009; Bijttebier et al 2009). Although in relatively recovered samples such as our own, dimensional symptoms (the duration of clinical symptoms) may have more relevance in determining diagnostic differences as opposed to diagnostic categories.

10.3. Tentative model

An amalgamation of this thesis findings is presented in a tentative model of eating disorders (see diagram 1). This model draws on influences from other theoretical models proposed by Treasures (in progress) 'Theoretical Model of Eating Disorders' (see chapter 1, section 1.6.3), Kaye's (2008) 'Neurobiological Model of Anorexia and Bulimia' and the 'Noradrenergic' Hypothesis' proposed by Nunn, Frampton and Lask (2012).

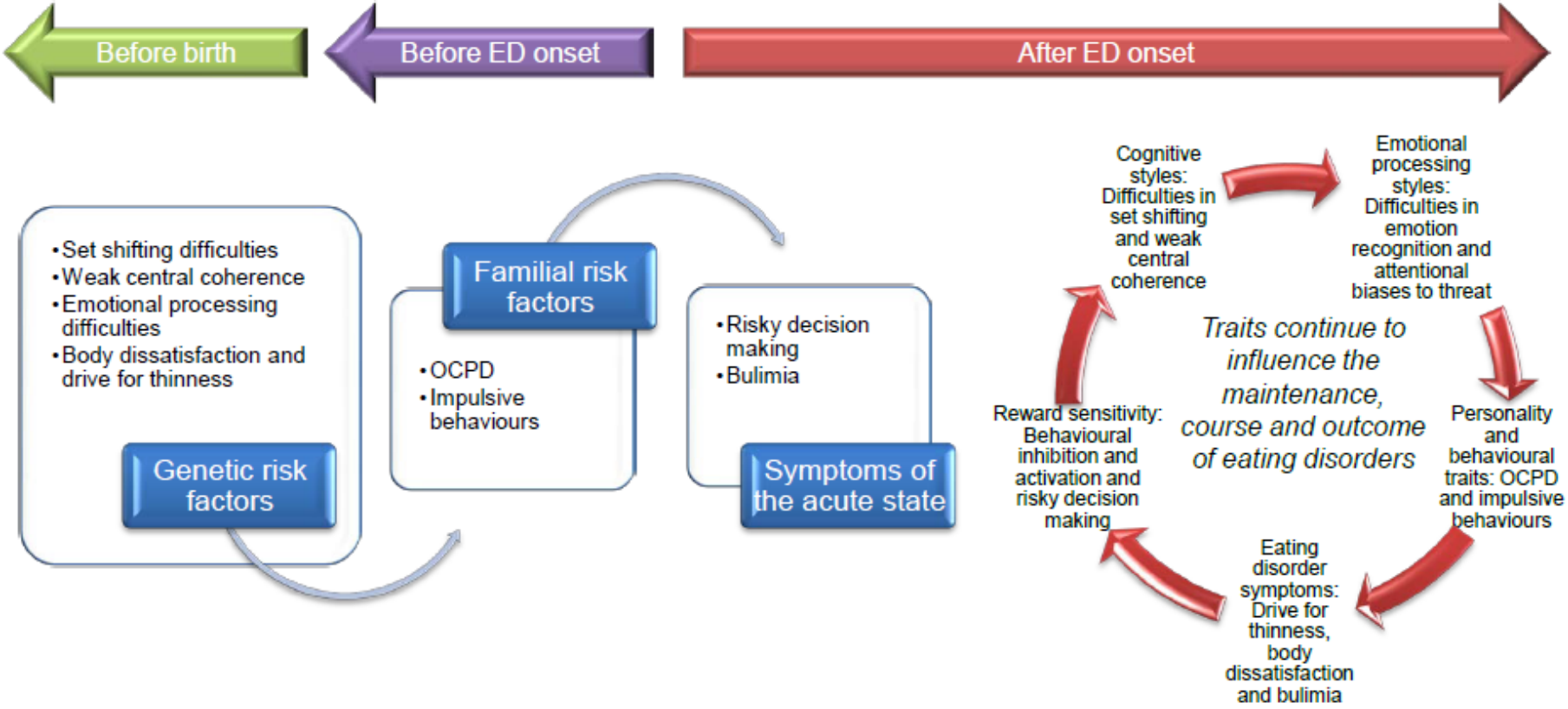
It is proposed that there exists a genetic predisposition which is moderated by epigenetic factors. According to Kaye (2008) premorbid traits include altered brain serotonin (5- HT) function that contributes to dysregulation of appetite, mood and impulse control in AN and BN as well as anxiety, obsessionality and inhibition in AN. In a similar way the 'noradrenergic hypothesis' proposes that a genetic predisposition for noradrenergic dysregulation is triggered by environmental factors and changes that occur during puberty. This contributes to dysfunction in the insula cortex. As a consequence, the neural circuitry between brain structures is impaired and this contributes to altered emotion and reward processing, difficulties in body size evaluation as well as obsessive compulsive behaviours, pervasive anxiety and impaired executive function in AN.

This thesis aimed to examine the genetic basis to some of these features. In doing so, it demonstrated differing genetic and environmental contributions to neurocognitive profiles, emotional processing styles and behavioural symptoms. This model (diagram 1) has simplified these findings by assigning each feature on the basis of which endophenotype criteria it satisfied most strongly. It proposes that set shifting difficulties, weak central coherence, emotional processing styles and psychological symptoms associated with eating disorders (i.e. drive for thinness, body dissatisfaction and bulimia) are part of the genetic predisposition to eating disorders. OCPD and impulsive behaviours are more environmentally influenced and may occur post-birth as a result of familial influences or prenatally as a consequence of

adversities experienced in the intrauterine environment. Reward sensitivity and bulimia may be more influenced by the acute state of eating disorders.

Post onset, these genetic and familial risk factors continue to interact with environmental factors (such as malnutrition and stress) to cause biological and epigenetic changes (Campbell et al 2011; Treasure, in progress). For example, in AN, starvation will continue to deplete the noradrenergic substances, increasing dysregulation and reinforcing the symptoms and disorder (Kaye, 2008; Nunn, Frampton and Lask. 2012). Other examples include the physical changes that occur during puberty which possibly interact with the insula dysfunction to cause an inaccurate homoncular representation of the body leading to a distorted perception (Nun, Frampton and Lask (2012). This may also include the alterations in neuroendocrine substances which occur as a result of starvation in AN (Grinspoon et al 1996) or binge-purge cycles in bulimic disorders (Monteleone et al 2002). These biological factors help to maintain the eating disorder and with time, alter the long term risk of it becoming a chronic condition. Although this model is based on data which is subject to its limitations (section 10.4), it may provide some suggestions for future research (section 10.6) and treatment (section 10.5).

Diagram 10.1: Tentative Model of Eating Disorders



10.4. General limitations of this report

A discussion of this thesis's broad limitations follows.

10.4.1. Sample size

The limited sample size of the clinical twin sample means that studies 2 to 7 were exploratory. Significantly larger samples sizes with sufficient statistical power would be required to conduct biometric model fitting analyses to estimate the exact contributions of 1) genetic, 2) shared or 3) unique environmental factors. The present research attributed within pair similarity in monozygotic twins to genetic factors on the assumption that they share on average 100% of genes. Firstly, it should be emphasised that the proportion of shared genes is merely an approximation due to the influence of epigenetic factors. Moreover, various other factors could contribute to concordance within identical twin pairs. These include shared environmental factors, especially adversities in the intrauterine environment. Within pair similarity may have also been encouraged by more similar interactions with their environment (i.e. interactions with peers or teachers) as a natural product of their identical physical appearance.

Furthermore, it is noted that our dizygotic twin sample was small. Therefore the interpretations of heritability were tentatively drawn. This was due to the practical difficulties of obtaining a dizygotic twin sample. Others have also highlighted the difficulty in obtaining dizygotic twins due to numbers declining over the past 50 years (Hur, McGue and Lacano, 1995). It may also be that dizygotic twins have less investment in their twin identity owing to their physical dissimilarity and are therefore less likely to join a twin registry.

10.4.2 Age

The greatest proportion of our twin samples was recruited from the UK twin registry. As previously mentioned the UK twin cohorts' average age is 45 years, which may account for the older age of our sample (Spector and Williams 2006). Attention is drawn to the non-ED cotwins who were substantially older than the proband group and controls. Although age was included as a covariate, this factor may have contributed to set shifting difficulties in this group, since neurocognitive impairments are known to increase with age (Ridderinkhof et al 2002; Ardila et al. 2000). Ridderinkhof et al (2002) found that older adults (mean age: 68.1) were less able to use explicit shift cues (either nonspecific or specific) on the WCST. It was concluded that set shifting difficulties increase with age, although other traits measured by the WCST, such as rule-induction or performance-monitoring abilities do not deteriorate as much (Ridderinkhof et al. 2002). The relationship between increasing age and set shifting difficulties appears to be influenced by years of education (Ardila et al. 2000).

Emotional processing deficits are also known to increase with age as a consequence of deficits in executive function (Garcia-Rodriquez et al 2011). In regard to the effect of age on the game of dice task performance (Brand et al 2005a), deficits in neuromodulation are known to increase with age and this may contribute to difficulties in decision making when reward information is uncertain (Eppinger, Hammerer and Li, 2011). In the Game of Dice task the reward information is made explicit at the outset. Therefore it is uncertain whether age associated deficits in dopaminergic and serotonergic neuromodulation will have influenced performance.

10.4.3. Diagnosis

Recruiting twins through the UK twin registry allowed for the inclusion of individuals with eating disorders across a broad spectrum of the illness, in terms of type, illness state and severity. Our relatively mixed sample of BN and BED (47.2%) and almost equal proportion of AN (52.8%) is taken into account when interpreting the findings. At present, the neurocognitive and behavioural profile of BED has received less investigation and a recent review has found no consistent profile in BD (Van den Eynde, 2010).

This recruitment method also minimised the likelihood of selection bias towards those with chronic eating disorders. For our proband group, only 41.5% had received treatment which meant that the ascertainment of participants differed from previous studies that have recruited from inpatient units. Those that never reach the attention of hospital services represent an understudied group. In addition, those that recover from eating disorders may represent a different class of the disorder to those that remain chronically ill. The more chronic and severe forms of eating disorders tend to have the greatest impairments in cognitive and emotional processing styles (Harrison, 2010).

For our probands it is noted that 64% (n=34) reported a recovery from having an eating disorder. In comparison, the vast majority of research has examined neuropsychological performance in participants who have a current eating disorders diagnosis. Since the current sample included people who were recovered from the illness, the neuropsychological and behavioural features under investigation were not necessarily associated with a current illness state. The observed features may be a consequence of having been ill previously or represent premorbid traits that contributed to developing an eating disorder. Our descriptive analysis which compared probands with a normal BMI with probands who were currently underweight confirms that many of the traits (set shifting difficulties, attentional biases to social affective stimuli, weak central coherence and reward sensitivity) are pronounced in the acute state (Roberts et al 2010; Tenconi et al 2011; Harrison et al 2010c; Harrison and colleagues,

unpublished data). This may account for our relatively smaller effect sizes for comparisons between probands and controls.

It is also noted that less monozygotic twins were currently recovered (i.e. 56.1%) in comparison to dizygotic twins (83.3%), which may have influenced the analysis of heritability. Nevertheless the number of probands that were currently underweight (BMI<18.5) were only marginally greater in the monozygotic group (14.6 %) in comparison to the dizygotic (0%) group. Another factor that may have contributed to the smaller differences between groups is the variability in neuropsychological profiles within the broad group of AN (Rose, Frampton and Lask, 2011; Harrison 2010). A case series of nine female patients with AN has shown a broad spectrum of strengths and weakness in set shifting, central coherence and visuospatial memory (Rose, Frampton and Lask, 2011). In a cohort analysis, such as our own, these subgroup differences would be masked. A comprehensive subgroup analysis was beyond the scope of the present thesis, due to the limited sample size and its primary focus on identifying endophenotypes.

10.4.4. Recruitment Bias

The use of a volunteer twin registry is a potential source of sampling bias, since it requires that the twins contact the registry themselves. Thus those who are more invested in being a twin may be more likely to volunteer (Bulik et al. 2000). This also makes it unlikely that twin pairs who have a less close relationship will participate which limits the generalisability of our results.

It may also be queried as to whether this sample is representative of the singleton population of eating disorders. Obstetric complications in twin samples have been associated with an increased risk of AN (Foley et al 2001). Secondly, sibling interaction (i.e. shared environmental factors) may differ between dizygotic and monozygotic twins as a result of their non identical and identical physical appearance. Research into the heritability of certain traits being attributed to sibling interaction and associated competitiveness has found it to be a negligible factor (Rebollo and Boomsma, 2006).

10.4.5. BMI

The clinical group of probands were a mix of those currently underweight (36%) and normal weight (64%). This factor may have influenced the thesis's findings. One study has reported that BMI is positively correlated with neuropsychological function (measured by the TMT-A task) (Mathias and Kent, 1998). However there is also evidence to support that poor set shifting abilities persists in patients with AN after weight recovery (Tenconi et al 2010) and other studies have found no association between BMI and performance on the Brixton task (Tchanturia et al 2011). Furthermore each neuropsychological trait may be differentially

influenced by a low BMI. For example set shifting difficulties appear to attenuate more with weight recovery in AN (Tchanturia et al 2011) than weak central coherence (Tenconi et al 2010; Harrison et al 2011).

In sum, it is very difficult to determine exactly how BMI influences neuropsychological function, since BMI is a clinical feature that is closely entangled with the symptoms of AN (Abbate-Daga et al 2011). Since the vast majority of neuropsychological studies (Tchanturia et al 2004; Tchanturia et al 2007) investigating these features have not controlled for BMI it was chosen to follow this methodology and allow the present findings to be interpreted within the current evidence base.

10.4.6. Confounding variables

This study was limited by not having systematically assessed environmental factors from conception to present day due to the time constraints on the assessment battery. A systematic assessment of environmental factors may have provided useful information with regard to the large discordances in neurocognitive and behavioural performance within identical twin pairs. Environmental factors could include peer group experiences, schooling and parenting styles and also adverse prenatal events. The Barker and Osmond (1986) hypothesis proposes that early life events which occur in the intrauterine environment may cause subsequent epigenetic changes that could influence the propensity for a number of conditions as well as eating disorders or risk traits. A measure that is recommended for future research is the Oxford Risk Factor Interview for Eating Disorders (ORFI) (Fairburn et al, 1997). This measures a variety of specific risk factors associated with EDs such as parental EDs, obesity, parental depression and alcohol and substance dependence.

Due to the constraints of the sample size, we chose not to exclude those with depression in our clinical sample, Although this is a common comorbidity in eating disorders, it is acknowledged that depression can amplify deficits in neurocognitive function and may have influenced our findings (Gotlib and Joorman, 2010; McClintock et al. 2010).

10.4.7. Battery of measures

There are several issues relating to the battery of tasks used in this thesis that have been discussed within their respective chapters. The main difficulty relates to the time constraints of the battery which meant that additional measurements which may have added important details to this study were excluded from the protocol to reduce the burden on participants. These included data of the delay and accuracy aspects of the ROCF which could have explained the much weaker central coherence found in unaffected twin siblings. Nevertheless, the overall

similarity within monozygotic twins validates the external validity of the set shifting, central coherence and emotional processing tasks.

10.4.8. Ecological validity

The neuropsychological and behavioural assessments were conducted in a laboratory setting by two researchers. A standardised procedure, quiet setting and limited distractions allowed for the control of extraneous variables. However it is uncertain to what extent these features such as set shifting difficulties measured by the WCST, are predictive of behaviours in the real world, such as inflexibility or difficulty coping with change. In light of this, a study which failed to find significantly more perseverative errors on the WCST in adolescents with AN, did find significantly more difficulties in cognitive and behavioural set shifting measured by a self report measure (Behavior Rating Inventory of Executive Function-Self Report) (McNarney et al 2011). Virtual environments may be an effective solution to increase ecological validity. One study which measured set shifting abilities in a virtual environment found performance to be significantly correlated with that in the real world (McGeorge et al 2001)

In the present research, attempts were made where possible, to use ecologically valid stimuli. Emotional processing was measured in response to ecologically valid stimuli, which is faces depicting emotions (Estroop and RME task). Such methods may have more accuracy than self-report measures of emotional processing such as the DERS, which are subject to the participants' own appraisal and social desirability bias.

10.4.9 Transdiagnostic analysis

Eating disorders are unstable longitudinally which inevitably creates diagnostic difficulties for genetic and epidemiological studies of psychiatric disorders (Helder and Collier, 2011; Rice et al 1992). One of the strengths of this research is that a dimensional account of eating disorders was taken over time as opposed to simply classifying them on the basis of a current category. This was executed by taking measurements of the duration of clinical symptoms (weighted by age) and devising a composite lifetime diagnoses based on the diagnostic phases over the life course. The findings suggest that the duration of clinical symptoms over time may have more clinical relevance than the use of a categorical diagnosis.

10.5. Clinical implications

The following section describes how knowledge presented within this thesis may add to the translational research evidence base and could be utilised by clinicians in treatment settings and for aetiological diagnosis.

10.5.1. Addressing traits in therapy

At present the Maudsely Model for Treatment for Adults with Anorexia Nervosa (MANTRA) is investigating the treatment outcome of therapies tailored towards specific neuropsychological and personality traits in anorexia nervosa. A pilot study has shown that MANTRA is successful in increasing BMI to a normal range, improving psychological functioning in 26% and improving scores on the eating disorder examination (EDE) to within 1 standard deviation from the community norm (Wade, Gilcrest, Treasure and Schmidt, 2010). This demonstrates the effectiveness of addressing specific cognitive styles and emotional processing in treatment.

The findings of genetic risk may inform clinicians of treatment response and allow them to assign achievable and realistic goals. Traits that demonstrated a substantial genetic basis such as attention to detail (measured by the central coherence tasks) may have a slower treatment response in comparison to those with a lower genetic basis such as risky decision making.

10.5.2. Neuropsychological feedback module

The neuropsychological feedback module requires the patient to complete a neuropsychological assessment (which lasts approximately 60 minutes) as part of their initial psychiatric assessment (Lopez, Roberts, Tchanturia and Treasure, 2008e). Subsequently the patient receives feedback on their neuropsychological profile. Patients who display anomalies in their neuropsychological profile (i.e. scores of 1 standard deviation away from the control population mean in more than two neuropsychological tasks) are provided with additional treatment sessions. The additional psycho-education sessions involve a formulation that describes the contribution of their neurocognitive traits to their AN symptoms.

This module may one day be used for the genetic screening of AN. Also there is potential for this module to include information regarding the genetic risk of traits, especially those that appear to be more heritable such as emotional processing and central coherence. This may help to reduce the stigma associated with certain behaviours and blame felt.

The benefits of this neuropsychological feedback module are that it is highly tailored to the individual's central coherence and set shifting abilities. This module could look to broadening its assessment to other traits, namely reward sensitivity and emotional processing. In addition, it could be expanded to treat those with bulimic disorders since it currently focuses on anorexia nervosa.

10.5.3. Cognitive remediation therapy (Tchanturia, Davies and Campbell, 2007).

Cognitive remediation therapy (CRT) involves a series of cognitive exercises to encourage adaptive cognitive strategies. It is proposed that reflection on strategies used to complete the

tasks, increases neural connectivity in the brain (Tchanturia, Davies and Campbell, 2007). CRT improves flexible thinking and global integration which can prime the patient to subsequently receive a more intensive psychological intervention such as cognitive behavioural therapy (CBT) (Tchanturia, Whitney and Treasure, 2006; Tchanturia, Davies and Campbell, 2007; Tchanturia et al., 2008). CRT has also proven to be successful when delivered as a group intervention in adults (Genders & Tchanturia, 2010) and adolescents with AN (Wood, Al-Khairulla and Lask, 2011). CRT may be particularly useful for attenuating traits with a substantial genetic basis that may have a more resistant response to treatment.

10.6. Future directions

10.6.1. Larger genetic studies

This thesis should be seen as a preliminary investigation that informs the design of prospective and more advanced studies. With larger samples the next step forward for genetic studies is to identify which of these endophenotypes are optimal risk indicators of eating disorder development. Glahn et al (2012) has devised a rigorous method to index the genetic utility of endophenotypes: "Endophenotypes ranking method" (ERV) (see below: formula to calculate endophenotype index). The value varies between 0 and 1 and higher values indicate that the endophenotypes is genetically correlated with the illness (i.e. a higher proportion of shared genetic factors that influence both the endophenotype and the risk for the illness). An endophenotype with a high ERV will more accurately predict the genetic risk of the disease than an endophenotype with a low ERV. Unfortunately this calculation is beyond the scope of this thesis primarily since the limited sample size means that we are unable to calculate the genetic correlation between the illness and endophenotype. Larger samples of twins with eating disorders would allow for us to rank these endophenotypes. However the practical difficulties of obtaining this unique sample are noted. Glahn et al (2012) have demonstrated that modern techniques involving high density typing will allow for large samples of unrelated individuals to estimate the parameters required for ERV. This makes the ERV estimation of endophenotypes in eating disorders a very realistic goal for future research.

Formula to calculate endophenotypes index (Glahn et al 2012):

$$ERV_{ie} = |\sqrt{h_i}^2 \sqrt{h_e}^2 \rho_g|$$

hi^2 : the heritability of the illness

he^2: the heritability of the endophenotype

^{2}Pg: the illnesses and endophenotypes genetic correlation

Nevertheless, some attempt has been made to diagrammatically represent how these traits could be ranked on the basis of the present research (Diagram 10.2a and 10.2b). The arrows indicate how many endophenotype criteria were satisfied: (1) associated with the illness, 2) familial risk and 3) heritable. The height of the arrow on the chart indicates how many endophenotype criteria the trait satisfies. The higher the arrow reaches, the more endophenotype criteria the trait satisfies.

Diagram 10.2: Endophenotypes for Anorexia Nervosa

	Childhood OCP traits	Impulsive behaviours	Set Shifting Brixton	Set Shifting WCST	Central Coherence GEFT	Central Coherence Rey	Emotional Processing Estroop	Emotional Processing RME	DERS	Game of Dice	BIS/BAS
Satisfies three endophenotype criteria				*Heritable + Familial + Illness*			*Heritable + Familial + Illness*				*Heritable + Familial + Illness*
Satisfies two endophenotype criteria	*Familial + Illness*	*Familial + Illness*			*Heritable + Illness*	*Heritable + Familial*		*Heritable + Illness*	*Familial + Illness*		
Satisfies one endophenotype criteria			*Heritable*								
Satisfies no endophenotype criteria											

Illness: The trait is present in those with an eating disorder history, suggesting that it is associated with the illness (effect size>= 0.3)
Familial: The trait is present in the unaffected twin siblings, suggesting it co-segregates within families (effect size>= 0.3)
Heritable: Monozygotic twins demonstrate greater within pair similarity in comparison to dizygotic twins, suggesting a genetic basis.

Diagram 10.3: Endophenotypes for Bulimic Disorders

	Childhood OCP traits	**Impulsive behaviours**	**Set Shifting Brixton**	**Set Shifting WCST**	**Central Coherence GEFT**	**Central Coherence Rey**	**Emotional Processing Estroop**	**Emotional Processing RME**	**DERS**	**Game of Dice**	**BIS/BAS**
Satisfies three endophenotype criteria				*Heritable + Familial + Illness*			*Heritable + Familial + Illness*				*Heritable + Familial + Illness*
Satisfies two endophenotype criteria	*Familial + Illness*	*Familial + Illness*	*Heritable + Illness*		*Heritable + Illness*	*Heritable + Familial*			*Familial + Illness*		
Satisfies one endophenotype criteria								*Heritable*		*Illness*	
Satisfies no endophenotype criteria											

Illness: The trait is present in those with an eating disorder history, suggesting that it is associated with the illness (effect size>= 0.3)
Familial: The trait is present in the unaffected twin siblings, suggesting it co-segregates within families (effect size>= 0.3)
Heritable: Monozygotic twins demonstrate greater within pair similarity in comparison to dizygotic twins, suggesting a genetic basis.

10.6.2. Linkage and molecular genetic studies

A demonstration of heritability and association with the disorder is typically seen as a justification for further research to identify susceptibility genes that contribute to eating disorders. This could inform the genetic architecture of eating disorders and its' taxonomy. Future studies could investigate the molecular genetic basis of neuropsychological and behavioural traits. Additional data of brain activation patterns may be useful in identifying specific genes associated with these traits. This information could help to explain the wide variability in performance, with some participants displaying difficulties and others having 'normal' performance. The possibility of subgroups with varying neuropsychological profiles has been noted in adolescents with AN (Rose, Frampton and Lask, 2011). Future molecular genetic studies may chose to include neurocognitive profiling as additional covariates to delimit subgroups within anorexia nervosa. This may help to hone in on risk genes for AN. Such strategies have been previously adopted when using highly heritable symptoms such as self induced vomiting to determine a subset of families with which to perform linkage analysis. This found a susceptibility locus for BN on chromosome 10p (Bulik et al 2003).

At present there has been two published Genome Wide Association Studies (GWAS) of AN. The first included a genome-wide case–control association study of 331 AN cases, 125 BN cases and 872 controls in a Japanese cohort (Nakabayashi, et al 2009). The findings showed 7 SNPs from the 1q41 locus and 3 SNPs from the 11q22 locus to be significantly associated with AN (before correcting for multiple-testing). However these SNPs were not associated with BN suggesting a different genetic aetiology (Nakabayashi, et al 2009). The second GWAS included 1,033 cases with AN and 3,773 controls. No single-nucleotide polymorphisms (SNPs) were significantly associated with AN (Wang et al 2011). Currently being conducted is a GWAS funded by the Wellcome Trust Case Control Consortium 3 (WTCCC3) including 3,000 cases with AN from 15 countries. Boraska and colleagues (to be submitted) have made some progress in examining genotypes associated with psychological symptoms and behaviours associated with eating disorders. These include the EDI subscales (Garner, 2004) and OCP traits (measured by the childhood retrospective perfectionism questionnaire; Southgate et al 2008). A study of 3,333 individuals of European ancestry detected genetic variants at a significance level of $p<10\text{-}5$ (not quite genome wide significance). The SNP rs7624327 which lies between the CCNL1 and LEKR1 genes was found to be significantly associated with bulimia (Boraska et al, to be submitted). Previously, variants near these genes have been associated with fetal growth and birth weight (Freathy et al 2010). Furthermore a meta-analysis of the 'discovery' cohort used by Borsaka and colleagues (to be submitted) and replication cohorts found an association between drive for thinness and two SNPs ($p<10\text{-}4$). These included the rs6265 in the BDNF gene which has been previously associated with AN and the rs10501087 located in the BDNFOS gene which has been previously associated with BMI. OCP

traits showed an association with the SNP rs1898111 that lies within the SEMA6D gene. Previously this gene has been linked with the neural wiring of the central nervous system (Leslie et al 2011). Furthermore OCP traits were associated with the SNP, rs10519201, located in the SHC4 gene. Previously, this gene has been associated with major depressive disorder in females in a Dutch sample (Aragam, Wang and Pan, 2011).

10.6.3. Longitudinal studies

Longitudinal studies are another method to explore traits that may increase the risk of developing eating disorders. Such studies can be expensive, lengthy and have methodological and practical implications (i.e. dropout rates and long term patient engagement). However this type of study design is particularly strong and can yield fruitful results. At present there is a cohort of women with anorexia nervosa that are being examined as part of a longitudinal study. This has shown that women with AN and comorbid ASD features tend to have poorer psychosocial functioning (measured by the Modified Morgan Russell scales; Ratnasuriya et al 1991 and the General assessment of functioning scale according to DSM-IV criteria) and a longer duration of illness (Wentz 2001; Wentz, 2005). This longitudinal study does not distinguish whether these ASD features occurred premorbidly or were encouraged by the acute state of AN. Future studies could look to investigate these traits as premorbid risks in a longitudinal study.

Perinatal risk factors are currently being examined as part of the ALSPAC cohort study (Avon Longitudinal Study of Parents and Children). This study is currently investigating the physical and psychological development of children born to women with eating disorders. This study will examine the effects of maternal eating disorders during pregnancy that may contribute to the vulnerability of eating disorders in their offspring (Kohari, Micali and Treasure, in progress). Such relationships could potentially imply epigenetic changes in the foetus as a consequence of a maternal eating disorder. The effects of epigenetic changes are potently demonstrated by the Dutch famine in 1944-45. Research has indicated that grandchildren of women who were pregnant during this period have a reduced birth weight (Painter et al 2008)

10.7. Concluding comment

This thesis presents an exploration of the genetic basis of neurocognitive and behavioural traits in twins with and without eating disorders. It builds on the growing evidence base which provides support for neurocognitive and behavioural traits associated with eating disorders being familial risk factors (Tenconi et al 2010; Roberts et al 2010; Roberts et al submitted). To the best of our knowledge, this is the first study in the field of eating disorders to adopt twin methodology to parse out the effects of genes alone on these traits. This thesis employed criteria as outlined by Gottesman and Gould (2003) to investigate the 1) eating disorder

symptoms, 2) childhood OCP traits and impulsive behaviours 3) neurocognitive traits such as cognitive inflexibility (set shifting difficulties) and 'attention to detail' (or weak coherence), 4) emotional processing traits such as emotion recognition and selective attention to social emotional stimuli and 5) reward sensitivity as endophenotypes of eating disorders.

The results provided evidence of a substantial genetic contribution to psychological symptoms associated with eating disorders and its' prognosis in a clinical and representative sample of twins respectively. Secondly OCPD traits and impulsive behaviours appeared to be associated with eating disorders and largely accounted for by familial factors which include shared genes and environmental factors. Thirdly, there appeared to be a substantial genetic contribution to the neurocognitive and emotional traits. In addition there were varying levels of a familial risk and an association with the illness. Fourthly, reward sensitivity was associated with bulimic disorders but there was less evidence to support a genetic basis. Lastly, behavioural activation and inhibition appear to be associated with eating disorders and demonstrated a familial and genetic basis.

With its emphasis on heritability, this thesis has begun to explore whether the neurocognitive and behavioural profile could be a premorbid trait that increases the risk of eating disorder development. The constraints of the sample size meant that all the conclusions were tentatively drawn. Nevertheless, there was evidence of some endophenotype criteria being satisfied for both cognitive and emotional processing traits. It is acknowledged that the somewhat small sized differences between clinical and control samples, owing to within group variation, differences across age groups and across the diagnostic spectrum, may restrict the ability of these measures to inform the future diagnosis and taxonomy of eating disorders. However the present findings may be used to inform new investigations for potential endophenotypes as well as prospective molecular genetic studies.

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Appendices

Appendix 1.1: Twin status questionnaire 'peas in a pod'

TWIN STATUS

With every questionnaire we need to ask the following questions so that we can determine whether new twins completing questionnaires for the first time are identical or non-identical.

Q1. I am … (1) ❒ Male (2) ❒ Female

Q2. My twin is… (1) ❒ Male (2) ❒ Female

Q3. At school, did people have trouble telling you apart?

(0) ❒ Yes (2) ❒ No (1) ❒ I don't know

Q4. Were your parents able to tell you apart at school age?

(2) ❒ Yes (0) ❒ No (1) ❒ I don't know

Q5. Were your close school friends able to tell you apart at school age?

(2) ❒ Yes (0) ❒ No (1) ❒ I don't know

Q6. Were strangers able to tell you apart at school age?

(2) ❒ Yes (0) ❒ No (1) ❒ I don't know

Q7. In childhood, which of the following would best describe you and your twin? (Please select one):

(0) ❒ As alike as peas in a pod

(2) ❒ Ordinary sibling likeness (like sisters or brothers)

(1) ❒ I don't know

Appendix 1.2: The eating disorder inventory II (EDI-2)

A = ALWAYS U = USUALLY O = OFTEN S = SOMETIMES = R = RARELY N = NEVER

		A	U	O	S	R	N
1.	I eat sweets and carbohydrates without feeling nervous						
2.	I think my stomach is too big						
3.	I eat when I am upset						
4.	I stuff myself with food						
5.	I think about dieting						
6.	I think that my thighs are too large						
7.	I feel extremely guilty after overeating						
8.	I think that my stomach is just the right size						
9.	I am terrified of gaining weight						
10.	I feel satisfied with the shape of my body						
11.	I exaggerate or magnify the important of weight						
12.	I have gone on eating binges where I felt that I could not stop						
13.	I like the shape of my buttocks						
14.	I am preoccupied with the desire to be thinner						
15.	I think about bingeing (overeating)						
16.	I think that my hips are too big						
17.	I feel bloated after eating a normal meal						
18.	I eat moderately in front of others and stuff myself when there gone						
19.	If I gain a pound, I worry that I will keep gaining						
20.	I have the thought of trying to vomit in order to lose weight						
21.	I think that my thighs are just the right size						
22.	I think my buttocks are too large						

23.	I eat and drink in secrecy						
24.	I think that my hips are just the right size						
25.	When I am upset, I worry that I will start eating						

Appendix 1.3: Demographic questionnaire

Participant No:

The information that you give us on this sheet will be treated as strictly confidential.

Your contact details on this sheet will be kept separate from the responses you provide in the following questionnaire. Only the lead researcher will have access to the file that links your identification details with the following questionnaire.

Thank you for participating in this study.

Name: ……..
Address: ……..

……

Postcode: ……

Tel (home):…… Mobile: ……
Email:……

YOUR DETAILS

Today's Date: _ _/ _ _ / _ _

Date of birth: _ _/ _ _ / _ _ Age: __ __ Sex: ☐ Male ☐ Female

Is English your first language? Yes / No

If no, from what age ?…… …

What is your ethnicity?

- ❍ **White British**
- ❍ **White Irish**
- ❍ **Other White**
- ❍ **Mixed White and Black Caribbean**
- ❍ **Mixed White and Black African**
- ❍ **Mixed White and Asian**
- ❍ **Other Mixed**
- ❍ **Asian or Asian British – Indian**
- ❍ **Asian or Asian British – Pakistani**
- ❍ **Asian or Asian British – Bangladeshi**
- ❍ **Other Asian**
- ❍ **Black or Black British – Caribbean**
- ❍ **Black or Black British – African**
- ❍ **Other Black**
- ❍ **Chinese**
- ❍ **Other ethnic group-_____**

Have you participated previously in research at the Eating Disorders Unit? Yes / No

If yes, please give details……

Are you currently receiving any medication? Yes / No

If yes, please give details(duration/usage)…… … …

Have you ever been diagnosed with a visual impairment? Yes / No

If yes, is this corrected with an aide? (e.g. glasses, contact lenses) Yes / No

Have you ever been diagnosed with a neurological condition? Yes / No

If yes, please give details……..

Have you ever had a head injury? Yes / No

If yes, please give details……..

Have you ever been diagnosed with a learning disability? Yes / No

If yes, please give details……..

Have you ever been diagnosed with epilepsy? Yes / No

If yes, please give details……..

What is you current employment status?

- ☐ Full time
- ☐ Part time
- ☐ Unemployed
- ☐ Student
- ☐ Retired
- ☐ Sick leave
- ☐ House wife / husband
- ☐ Other ……..(please specify)

What is your current or most recent occupation?

……..

If you are unemployed, please indicate for how long you have been unemployed for and what your previous occupation was:

Unemployed for: ……..

Previous occupation: …….

What is the highest level of education you completed?

- ☐ No qualifications
- ☐ O Level / GCSE
- ☐ A Level / NVQ
- ☐ Diploma / BTEC
- ☐ University Degree
- ☐ Postgraduate Degree
- ☐ Other……...(please specify)

How many years of education have you received (from age 5) ? ……..

Have you ever had eating difficulties? Yes / No

Have you had to take time off from school or work due to your eating difficulties? Yes / No
If Yes, how long in total? ……..

Have you had a previous hospital admission for your condition? Yes/No
If so, how many? ……

For how many years have you had an eating disorder? .....

What is the lowest ever BMI you have been? ……

What is the highest ever BMI you have been? **……**

Do you have a twin? Yes / No

If yes, are you identical or non-identical twins ?..... … … … …
What is their name (email address) ? ……
How long have you lived with them?…… …

Are you adopted? Yes / No

What is your marital status?

- ☐ Married
- ☐ Living together
- ☐ Single
- o In a relationship
- ☐ Divorced
- ☐ Separated
- ☐ Widowed

How many children do you have?

a) No. of daughters: _____ b) their ages: ____; ____; ____; ____; ____
c) No. of sons: _____ d) their ages: ____; ____; ____; ____; ____

Are you currently pregnant? Yes / No

Who lives in your household with you? (e.g. mum, brother, 2 friends)

……..
Has anyone in your family been diagnosed with a psychiatric condition? Yes / No
If yes, please give details……..
What relation is this person to you?……..
Have you ever been diagnosed with a psychiatric condition? Yes / No

If yes, please give details……
What is your current weight?_____

What is your current height?_____

Appendix 1.4 National adult reading test – List of words

National Adult Reading Test – List of Words

NART ANSWER SHEET

Name : _____

Date : _____

Code : [ ]

WORD	ANSWER	WORD	ANSWER
CHORD		SUPERFLUOUS	
ACHE		SIMILE	
DEPOT		BANAL	
AISLE		QUADRUPED	
BOUQUET		CELLIST	
PSALM		FACADE	
CAPON		ZEALOT	
DENY		DRACHM	
NAUSEA		AEON	
DEBT		PLACEBO	
COURTEOUS		ABSTEMIOUS	
RAREFY		DETENTE	
EQUIVOCAL		IDYLL	
NAIVE		PUERPERAL	
CATACOMB		AVER	
GAOLED		GAUCHE	
THYME		TOPIARY	
HEIR		LEVIATHAN	
RADIX		BEATIFY	
ASSIGNATE		PRELATE	
HIATUS		SIDEREAL	
SUBTLE		DEMESNE	
PROCREATE		SYNCOPE	
GIST		LABILE	
GOUGE		CAMPANILE	
ERRORS		**ERRORS**	
IQP / **IQV** / **IQPe** / **R**		**TOTAL**	

Appendix 1.5: The eating disorder diagnostic scale (EDDS)

Please read all the questions carefully.

We would like you to think of a **3 month period in your life** when your concerns about your weight and shape were at their strongest.

When was this period (months/year) _____

During this 3 month period….

	Not at all		Slightly		Moderately		Extremely
1. Did you feel fat?	0	1	2	3	4	5	6
2. Did you have a definite fear that you might gain weight or become fat?	0	1	2	3	4	5	6
3. Did your weight influence how you thought about (judged) yourself as a person?	0	1	2	3	4	5	6
4. Did your shape influence how you thought about (judged) yourself as a person?	0	1	2	3	4	5	6

During this 3 month period when your concerns about weight and shape were at their strongest…

5. Were there times when you felt that you ate what other people would regard as an unusually large amount of food (e.g. a quart of ice cream) given the circumstances? **YES NO**

6. During the times when you ate an unusually large amount of food, did you experience a loss of control? (feel you couldn't stop eating or control what or how much you were eating)?

   YES NO

7. How many DAYS per week on average (during that 3 month period) did you eat an unusually large amount of food and experience a loss of control?

   0 1 2 3 4 5 6 7

8. How many TIMES per week on average (during that 3 month period) did you eat an unusually large amount of food and experience a loss of control?

   0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

During these episodes of overeating and loss of control did you…

9. Eat much more rapidly than normal? **YES NO**

10. Eat until you felt uncomfortably full? **YES NO**

11. Eat large amounts of food when you didn't feel physically hungry? **YES NO**

12. Eat alone because you were embarrassed by how much you were eating? **YES NO**

13. Feel disgusted with yourself, depressed, or very guilty after overeating? **YES NO**

14. Feel very upset about your uncontrollable overeating or resulting weight gain? **YES NO**

15. Did you experience these episodes of overeating and loss of control for a period longer than 3 months? **YES NO**

    a. If YES, for how long did these episodes continues (please circle):
        i. Between 3 and 5 months
        ii. 6 months of longer

During the 3 month period when your concerns about weight and shape were at their strongest…

16. How many times per week on average did you make yourself vomit to prevent weight gain or counteract the effects of eating?

    0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

17. How many times per week on average did you use laxatives or diuretics to prevent weight gain or counteract the effects of eating?

    0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

18. How many times per week on average did you fast (skip at least 2 meals in a row) to prevent weight gain or counteract the effects of eating?

    0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

19. How many times per week on average did you engage in excessive exercise specifically to counteract the effects of overeating episodes?

    0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

20. How much do/did you weigh? (If uncertain, please give your best estimate):

a. Currently	_____	Stones	_____	Lbs	OR	_____	Kg
b. During the 3 month period when your concerns about weight and shape were at their strongest	_____	Stones	_____	Lbs	OR	_____	Kg
c. Heaviest weight at your current height. Age _____	_____	Stones	_____	Lbs	OR	_____	Kg
d. Lightest weight at your current height. Age_____	_____	Stones	_____	Lbs	OR	_____	Kg

21. How tall are you? _____ ft _____ins OR _____ m _____cm

At the time when your concerns about your weight were the strongest:

22. Did you miss your menstrual period for 3 months or longer? **YES NO N/A**

23. Were you taking birth control pills? **YES NO N/A**

Please indicate whether any of the responses you have given about your eating behaviour refer to:

24. A period within the past year **YES NO**

25. A period including the past month **YES NO**

Appendix 1.6: EATATE lifetime diagnostic interview

EATATE LIFETIME INTERVIEW

Measurement of lifetime eating history for European Healthy Eating Project

This instrument is derived from the EDE, CIDI and LIFE EAT. The aim of the instrument is to measure a lifetime history of eating symptoms and those symptoms of OCD, OCDP and impulsivity which appear to be part of the phenotype so that research criteria for eating disorder diagnosis can be constructed as can partial cases. The instrument also measures obsessive compulsive disorder, obsessive-compulsive personality disorder and impulsivity over the lifetime. The aim of the interview is to measure objective behavioural symptoms as much as possible.

The symptoms are transferred for display onto a life history chart. Both the duration and the severity of symptoms are necessary for to fulfill research criteria. We recommend sharing the life history chart with the interviewee, so that it is completed as a joint endeavor.

Anchor points
The chart contains a space for anchor points. Birthdays are an obvious anchor point. Other significant events should be mapped onto the chart, as they will ensure that the time course of symptoms can be measured. These will include public examinations, change of school/job etc. In the case of overt anorexia nervosa episodes of treatment/ inpatient and outpatient should be recorded.

Current State
It may be helpful to construct the interview starting with the initial anchors of current status and time of onset i.e. focus on current symptoms and symptoms at onset and then construct change points during the course of the illness.

Onset
The timing of onset should be when the symptom severity reaches a degree of severity to be classified as clinical caseness. This is usually clear cut for anorexia nervosa as weight and amenorrhoea are reliable markers. There may be more uncertainty about the onset of bulimia nervosa.

Change Points
We are also interested in accurately defining change points e.g. when bingeing began, when vomiting began.

Context
Also it is helpful to have the context in which the symptoms changed e.g. during treatment when food controlled by others.

Symptom Definition
We have decided to follow the latest edition of the EDE and will measure objective (>1000 kcal) rather than subjective binges. Please fill in the frequency, as these criteria are uncertain for anorexia nervosa binge purge subtype.

Part 1 Interview

Thank you for agreeing to take part in this study. Before we start I would like to ask a few questions about you.

Section 1: Place of birth, nationality

What region /city did your family originate from?

Where were you born?	Country: ……Rural/ Town / City
Where were your parents born?	Country: ……..Rural / Town / City
Where were your grandparents born?	Country: ……Rural / Town /City

---

We are interested in mapping symptoms over time. In order to do this I need to construct a sort of life chart? I would like to mark important events in your life, which will help anchor the times. First what is your birthday. That will probably be a useful anchor point for each year. I will fill in your birthday for this year 200-. What is your age this year? Now I will go back to your 10th birthday and mark off the ages and dates in between as a rough skeleton of a life history. We may find that as the interview progresses we need to readjust things. That is normal and that is why we use this anchor sheet as an aide memoir. If necessary, we can extend the chart to the time before you were 10yrs old.

Now can we plot important change points in your life e.g. changing or leaving school, public exams, admissions to hospital etc.

- I would like to ask you about problems you might have had either with eating or with your weight. Have you ever had **a concern about your weight, your eating, or being too fat?** **NO☐ YES☐**
- Has your weight or shape ever had a profound effect on how you thought about yourself as a person? **NO☐ YES☐**
- What is your current weight? ……st …… lb …… kg
- What is your current height? …… ft …… in. …… cm

Current BMI (Kg/m^2) _____

Plot current weight on lifeline

Section 2: Weight Loss History

Please use the following probes to elicit weight history and record on the lifeline.

- Have you ever **lost a lot of weight**, that is, 10-12lbs/5 kg or more, or so that others were worried, either by dieting or without meaning to, (not by having a baby or an operation)? **NO☐ YES☐**

- How old were you the first time you lost 10-12lbs/5kg, or, so much weight that other people said that you were too thin? ……. Yrs

- When is the last time [that you lost that much weight or people thought you were too thin?] ……... Yrs
- Have there been other times [when you lost that much weight or people thought you were too thin?]
- What was your lowest weight during each of these episodes, how old were you when these episodes occurred and how long did they last?
- What was your weight before each of these episodes?
- What is the lowest weight you ever had after maturity and how old were you at that time? …….. st ……..lb / …… kg Age: …….Yrs
- What is the lowest weight you ever had after maturity? …….. st ……..lb / ……kg

- How tall were you then? ……...ft …….. in. /……. cm

Lowest ever BMI (Kg/m^2) _____

Plot lowest weight on lifeline

Total duration of underweight state (BMI<17.5) **..…… Months ……Years**

- Were people ever concerned that your weight was too low or that your growth was poor as a child? **NO☐ YES☐**
- What age were you then? ……. yrs
- Can you remember what weight and height were you then? …… st ……lb / ……..kg ……ft ……in./ ……..cm

Plot childhood lifeline

BMI card can be needed here.

If lowest ever BMI greater than 20, and no weight/growth concern in childhood skip to section 5 (page 5)

Section 3: Inappropriate weight concern

- At the time, when you lost a lot of weight/people said you were too thin, did your weight affect how you thought about yourself? **NO☐ YES☐**

- At that time, were you afraid that you would regain the weight? **NO☐ YES☐**

- At that time, did you still think you were too fat? **NO☐ YES☐**

- At that time, did you think some parts of your body were too fat? **NO☐ YES☐**

- At that time, did you ever avoid being in places where others could see your body, for example, in communal changing rooms, when swimming or wearing tight clothes? **NO☐ YES☐**

Inappropriate weight concern Total: **/5**

If scoring >/= 4/5 probe for time course of inappropriate weight concern and plot on lifeline. Whenever possible try to ask for examples of how these attitudes impinged on their behaviour or the lifes of others.

Section 4: Others concern about weight loss

- At that time, when your weight was at its lowest, did other people say that you were too thin? **NO☐ YES☐**
- At the time when you lost a lot of weight/people said you were too thin, did others tell you that your low weight was a hazard to your health? **NO☐ YES☐**

If yes to any of these questions plot "others concern" on lifeline.

Section 5: Weight Gain History

Please use the following probes to elicit weight history and record on the lifeline.

- Have you ever **gained a lot of weight**, that is, 10-12lbs/5kg or more, for any reason except pregnancy? (including weight gained gradually over a period of months)? **NO☐ YES☐**
- What is the heaviest weight you ever had at maturity (not because you were pregnant) and how old were you at that time?

  .....st .....lb / ..... kg Age:.....years
- How tall were you then? .....ft .....in. / ..... cm

Highest ever BMI (Kg/m^2) _____

Plot heaviest weight on lifeline
Calculate the BMI from the chart
If this weight gain is in the context of treatment for anorexia nervosa plot the relevant weights on the life chart and then skip to Section 8

If the maximum weight is less that BMI of 25kg/m2 skip to Section 8. (Page 7)

- Have relatives or friends ever been concerned/commented that you have gained weight? **NO☐ YES☐**
- How old were you the first time you gained 10-12lbs/5kg, or, relatives or friends commented that you had gained weight? ..... yrs
- When is the last time that you gained this much weight or, relatives or friends commented that you had gained weight?
- Have there been other times when you gained that much weight or relatives or friends commented that you had gained weight?
- Were you ever overweight or considered overweight by others, as a child? **NO☐ YES☐**
- Were people so concerned that they tried to do something about it? **NO☐ YES☐**

- How old were you when you were first overweight/considered overweight? ……...yrs

Plot weight changes on lifeline

Section 6:Concern Overweight

- At the time when your weight was at its heaviest/people were concerned about your weight, did you think you were too fat? **NO☐ YES☐**
- At that time, did your weight affect how you thought about yourself? **NO☐ YES☐**
- At that time, did you think some parts of your body were too fat? **NO☐ YES☐**
- At that time, did you wish to lose weight? **NO☐ YES☐**
- At that time, did you ever avoid situations where others would see your body, for example, in communal changing rooms, when swimming or wearing tight clothes? **NO☐ YES☐**

Concern overweight Total: /5

If scoring >/= 4/5 probe for time course of culture concordant weight concern and plot on the lifeline.
Only if scoring </= 3/5 ask the following questions:

Section 7: Others concern about over weight/weight gain

- At that time, when your weight was at its heaviest, did other people express concern about your weight? **NO☐ YES☐**
- At the time when your weight was at its heaviest/people were concerned about your weight, did others tell you that your weight was a hazard to your health? **NO☐ YES☐**

If yes to any of these questions plot "others concern" on lifeline.

Section 8: Binge Eating

- Have you ever had a time when you would eat unusually large amounts of food within a few hours, that is, eaten in binges? **NO☐ YES☐**
- How long would one of these binges last? (Minutes)……
- What kind of things would you eat during a typical binge?

RECORD:

……
……
……

Is this only a minimal amount of food (like a yogurt or one chocolate bar)? **NO☐ YES☐**

If YES, check out the next 3 questions first:

1. The total amount you may have eaten during one episode might be over a thousand calories? **NO☐ YES☐**
2. Has it ever been the case that if anyone off the street saw you eating this amount they would be shocked? **NO☐ YES☐**
3. Have you ever binged on alcohol on a regular basis? **NO☐ YES☐**
   How much per session and how may times a month? .....

If the answer to all of these is NO, skip to section 9 (page 8)

During these eating binges, have you felt that you were out of control?

1. Around the time when you were binge eating, did you spend a lot of time thinking about eating? **NO☐ YES☐**
2. Did you find it difficult to resist going on an eating binge? **NO☐ YES☐**
3. Have you ever felt that you had no control over what you were eating during an eating binge? **NO☐ YES☐**
4. Have you ever been afraid that you might not be able to stop one of these eating binges once you started? **NO☐ YES☐**
5. Have you ever had to do something special to make yourself quit one of these eating binges - like going to sleep, making yourself vomit, or leaving the house? **NO☐ YES☐**

Lack of control total: /5

During these binges have you:

a) eaten more quickly than normal? **NO☐ YES☐**
b) eaten until you felt excessively full or bloated? **NO☐ YES☐**
c) eaten a lot even though you weren't hungry? **NO☐ YES☐**
d) eaten alone because you felt ashamed? **NO☐ YES☐**

- *After your eating binges, have you:*

a) Hated yourself? **NO☐ YES☐**
b) Felt depressed or guilty because you have eaten so much? **NO☐ YES☐**

- Around the time when you were binge eating, was your self-esteem much more dependent on your body shape or weight than in other people? **NO☐ YES☐**

- Were you afraid that you would become too fat? **NO☐ YES☐**
- Did you think you were too fat? **NO☐ YES☐**

Total: /9

If scoring >/=2/5 for lack of control and >/=4/9 on the other questions, elicit lifetime course of episodes of bingeing.

If <2/5 for lack of control and >/=4/9 on the other questions, score as binge eating and plot this on life line.

Please record frequency of bingeing/overeating on the lifeline in *frequency per month.*

It may be necessary to elicit more anchor points to date changes in eating symptoms.

- When did you first binge eat in the way you have just described? …….. Age (yrs)
- How frequently did bingeing happen at that time?
- Have there been other times in your life when bingeing was a problem?

Continue enquiry to include all times when binge eating has been present.

Plot on the life chart.

Section 9: Weight control behaviours

The following section examines weight control strategies. Please probe to elicit time course and frequency of these behaviours and record all episodes on the lifeline as ***frequency per month.***

For any of the illicit behaviours ask about age when it first appeared, times when it was most severe and the duration of the behaviour.

You may need to elicit more anchor points in order to define when any change in symptoms occurred.
It is interesting to note whether others controlled the subject during these episodes e.g. inpatient treatment, family became active making her eat.

- Have you ever done anything regularly in order to keep from gaining weight, or to lose weight -- things like,

a) Exercising a lot? **NO☐ YES☐**

What did you do? How long would you do it for? How many days a week? Please specify typical example over an average 2-month period……...
……
At what age did you first start exercising to lose weight? …….. years
At what age range did you exercise regularly? From …… to ……. years old

The length of period when exercising was present: _____ years _____ months

b) Staying on a strict diet or following strict rules about the food you would eat? **NO☐ YES☐**

What were the rules that you followed? How many days a week did you stick to it? ……
……
At what age did you first go on a strict diet? ……years
At what age range were you on a strict diet? From …… to ……. years old

The length of period of strict dieting: ____ years _____ months

b) Fasting by not eating at all, or only taking liquids for eight hours or more?
NO☐ YES☐
Please specify:……
At what age did you fast to loose weight for the first time? …….years
At what age range did you fast regularly? From ……. to ……. years old

The length of the period when fasting was present: ____ years _____ months

c) Taking water pills or diuretics? **NO☐ YES☐**
How many times a month would you take these? ……times/month
Please specify:……

At what age did you use laxatives for the first time? …….. years

At what age range did you take water pills/diuretics? From …… to …. years old

The length of the period during which water pills were taken: ____ years _____ months

d) Taking laxatives or enemas? **NO☐ YES☐**

Please, specify (Please plot laxatives as total tablets used per month):……..
……
At age did you start to use them? ……. years
At what age range did you use them on a regular basis? From …… to ……. years old

The length of the period when laxatives/enemas were taken: ____ years _____ months

e) Taking other medicines or pills e.g. amphetamine, ecstasy, thyroxin, anabolic steroids, insulin, caffeine? (Only plot use of those that affect weight control and appetite, irrespective of reason given for use) **NO☐ YES☐**
Please specify:……
……
At what age did you start taking them? …… years
At what age range did you take them on a regular basis? From …… to …. Years

The length of the period during other medicines were taken: ____ years ____ months

f) Making yourself vomit? **NO☐ YES☐**

How many times a month would you vomit? ……..times/month
Please specify:……
……
At what age did you first vomit? …… years
At what age range did you vomit on a regular basis? From …… to …. Years

The length of the period when vomiting was present: ____ years ___ months

g) Other (e.g. >3 litres drink, sauna, chewing & spitting food) **NO☐ YES☐**
Please specify:……
At what age range did you use these behaviour? From …… to …. Years

The length of the period when other behaviour was present: ____ years ___ months

Section 10: Food Related Fear and Disgust

- Have there ever been times when you have eaten in secret (not including binges)? **NO☐ YES☐**
- Have there ever been times in your life when you have been unable to eat in front of other people (not including binges)? **NO☐ YES☐**
- Have you ever definitely wanted your stomach and guts to be empty? **NO☐ YES☐**
- Have you ever felt frightened or disgusted or ashamed by any foods? **NO☐ YES☐**

  Please specify food type:……

If YES,

- Has this fear, disgust or shame ever lead you to avoid that particular food? **NO☐ YES☐**

Total: /5

If scoring >/=3/5 please plot food related fear/disgust on the lifeline.

Section 11: Preoccupation with food:

- Has thinking about food or its calorie content ever made it much more difficult for you to concentrate on things you are interested in. For example, reading, watching TV, following a conversation? **NO☐ YES☐**
- Have you ever spent what other people would consider an unusually large amount of time on food related activities such as supermarket shopping, cooking or preparing food or reading recipes? **NO☐ YES☐**
- Have you ever stolen food, or money with which to buy food, for example from shops, food outlets, friends or family? **NO☐ YES☐**

Total: /3

If scoring >2/3 please plot preoccupation with food on the lifeline.

Section 12: Menstrual History

WOMEN ONLY:

What age were you when your periods started? ……. years

- Have you ever had 3 menstrual periods in a row, **within** a time frame of 3 months (e.g. first regular periods)?

NO☐ YES☐

If no, skip remainder

- How old were you when you had your first 3 menstrual periods in a row? …….. years
- Did you ever miss? **NO☐ YES☐**
- How old were you when you first missed? ……. years
- How long did you miss periods for? …… years ……..months
- Have there been other times when you have missed periods? **NO☐ YES☐**
- If yes, how old were you and how long did you miss them for?

Total duration of amenorhea: ……yrs …….months

- Did you ever use 'the pill' or any other hormonal contraceptive? **NO☐ YES☐**
- At what age range were you taking hormonal contraceptive? From ……..yrs to ……..yrs

Please specify, which ……

- Did you ever take hormonal replacement therapy? (for prevention of osteoporosis)

NO☐ YES☐

Total duration of use of hormonal contraceptives: ……. years

For interviewer: If the subject did not miss 3 menstrual periods in a row, was she on hormonal contraceptive during the period when her BMI was < 17,5?

NO☐ YES☐

Please plot menstrual history on lifeline (P = regular periods; I = irregular periods; A = amenorrhea; Ocp = pill taking; D = depot contraceptive)

- Have you ever been pregnant?

Please plot all pregnancies and their outcomes on the lifeline - (P= beginning of pregnancy; M=miscarriage; T=termination; S=still birth; L=live birth)

Section 13

MEN ONLY:

What age were you when you went through the changes of puberty? E.g. had a growth spurt, had morning erections, developed facial hair, voice breaking? …… yrs

Has there been a time when you have lost some of these changes eg you have not had an erection on waking in the morning on a regular basis or you have had to shave less frequently?

NO☐ YES☐

How old were you then? …….. years

Were there other times?

Plot on the lifeline.

Are there any other things that may be important if we consider you eating over time?

……

……

Family History

Did any members of your extended family have any of the eating symptoms we have just talked about? (please include partial syndromes, obesity and overeating)

If yes

Can you tell me a little more about that?
Probe symptoms sufficiently to complete summary diagnostic sheet for each affected relative.

Fill in diagnostic Sheet for each affected family member

Summary Eating Disorder History Sheet

Name _____ *Study Identification Number* _____ *Age* _____

Did the subject fulfill the criteria for AN?					**Yes**	**No**
Weight loss > 15% BMI < 17,5		yes	no			
Amenorrhoea > 3 months	OR	yes	no			
OCP taken when BMI < 17,5		yes	no			
Inappropriate weight concern		yes	no			
Others concern		yes	no			
Fear Food		yes	no			
Food preoccupation		yes	no	Age of onset	_____	

Was there a period of **restricting anorexia nervosa** (no binging or purging)? Yes No
From age _____ to age _____

Was there a period of **purging anorexia nervosa** (vomiting or laxatives)[not only in the context of enforced eating]? Yes No
From age _____ to age _____

Was there a period of **binging anorexia nervosa** [not only in the context of enforced feeding]? Yes No
From age _____ to age _____

Was there a period of **binge – purging anorexia nervosa** (binge eating and vomiting or laxatives)? Yes No
From age _____ to age _____

Did the subject fulfill the criteria for bulimia nervosa?

Bingeing > 24 times in a 3 month period when not at an anorexic weight? **Yes No**
At this time were vomiting or purging used for weight control? **Yes No**
Age of onset _____ until age _____

Did the subject fulfill the criteria for binge eating disorder? **Yes No**

Age of onset _____ until age _____

Did the subject fulfill the criteria for obesity (BMI =/> 25)? **Yes No**

Age of onset _____ until age _____

Did any relative have any evidence of an eating disorder? **Yes No**
Relative
Fill in a summary sheet for each additional relative

How accurate do you think the information you have got for this interview has been?

Very accurate Vague

Appendix 1.7: EATATE lifetime diagnostic interview Part II

2002

EATATELIFE PHENOTYPE

Date: _____

Interviewer : _____

Patients ID

Measurement of lifetime eating history for European Healthy Eating Project

Part 2 Interview: Childhood Perfectionism, Rigidity and Lifetime Impulsivity

The questions that I am now going to ask concern what you were like most of the time and how others might have seen you as a child. I am interested in what was typical of you throughout your childhood, not just recently. So when you answer these questions think back to what you were like as a child or adolescent before you developed an eating disorder (or before the age of 18 if eating disorder onset was after 18 years of age). You may have changed later in your life, but for these questions I am only interested in your childhood. I am particularly interested if friends or family or teachers noticed these things and if they ever caused comment or even difficulty or if you found that these traits got in the way of you having a good quality of life.

SCORING: In this section please write down/ audiotape examples.

Score 2 - if there is an obvious trait present that impinges overtly on the relationship of the subject with the world and with others (objectively defined).

Score 1 – if there is a possible trait but if it does not impinge on life or relationships greatly.

Score 0 – if trait is absent.

Perfectionistic Domain

Childhood Perfectionism

1. General Childhood Perfectionism

- In childhood did you have higher standards or were you more perfectionistic than those around you were? Did you regard other children as having unacceptable standards?
- In what way?
- Did you tend to take longer than others doing these things?
- How far would this interfere with other activities, like leisure time, friends?
- Did other people comment on the way you did things or your tendency to be perfectionistic?
- If yes: Could you please give me an example of this. Did other people ever comment on it?

1. General Childhood Perfectionism 2 ☐ 1 ☐ 0 ☐

2.What about school work?

- When you were at school, did you persist in trying to solve problems when most of your friends/classmates had given up?
- How much time would you spend on homework? Did you spend much longer on it than you needed to?
- Would you redo a piece of work if it had errors on it or if you had made even one mistake? How often did you do this?
- Were you always striving for the best grade and never feeling happy or content no matter how hard you had worked?

2. School Work Perfectionism 2 ☐ 1 ☐ 0 ☐

3. What about self care (grooming)?

- Did you spend a long time doing or redoing your hair to make sure it was straight without bumps etc.?
- Were you very particular about what you wore (e.g. getting ribbons matching your dress, making sure the colors you wore coordinated)?
- Were you particularly concerned about order & symmetry, hair, hem, cuffs?
- Did you spend a lot of time and effort on matters of personal hygiene (e.g. cleaning your teeth, washing your hands etc.)? [Is this ego syntonic?]
- Did other people comment? What did they say?
- How far would this interfere with other activities?

  Can you please give me examples?

3. Self Care Perfectionism 2 ☐ 1 ☐ 0 ☐

4. What about looking after your room?

- Did you spend a long time getting your room tidy and organized?

- Making sure that everything was "just so" and in its proper place?
- Were you particularly concerned about order and symmetry?
- Did other people comment? What did they say?
- How far would this interfere with other activities?

4. Order, Tidiness Perfectionism **2 ☐ 1 ☐ 0 ☐**

5. What about looking after pets?

- For example, did you feed them regularly, clean cages etc.?
- Would you take looking after pets to extremes?
- In what way? Can you give me an example? For example, would you diligently take your dog for a long walks no matter what the weather or your or your family schedule?
- Did other people comment? What did they say?
- How far would this interfere with other activities?

5. Pet Perfectionism **2 ☐ 1 ☐ 0 ☐ NA ☐**

6. What about hobbies?

- Did you feel that you had to put in a great deal of effort to be the best pop/film star fan?
- How far did you feel that you had to be the most knowledgeable person about particular things (e.g. TV show, story, pop group, football club)?
- Were you a keen collector as a child, or an expert on some topic?
- If you had a hobby such as playing a musical instrument / swimming/ ballet did you always put in supreme effort? Did you get any grades/awards? (What level and at what age?)
- Did other people comment? What did they say?
- How far would this interfere with other activities?

6. Hobby Perfectionism **2 ☐ 1 ☐ 0 ☐ NA ☐**

7. Other:

- Were there other areas in which you strove for perfection or the highest of standards?
- For example, trying to be the best daughter in the world or the best pupil?
- Did other people comment? What did they say?
- How far would this interfere with other activities?

7. Other areas Perfectionism **2 ☐ 1 ☐ 0 ☐**

8. Childhood Order, Symmetry (see clothes & room above) ***(SCORE ONLY)***

Note: Code item based on two questions from sections 3 & 4 asking about the drive for order and symmetry. Code 2 if either question is coded 2; otherwise code 0.

8. Childhood Order, Symmetry **2 ☐ 0 ☐**

9. Childhood Cautiousness

- Were you frightened of making a mistake as a child?
- *If yes*: Did that bother you or cause any problems for you?
- Can you give me examples about this?

9. Childhood Cautiousness **2 ☐ 1 ☐ 0 ☐**

10. Childhood Doubt

- When you were a child, did you have a lot of doubts about things?
- *If yes*: Did that bother you or cause any problems for you?
- Can you give me examples about this? E.g. food choice, clothes choice

10. Childhood Excessive Doubt **2 ☐ 1 ☐ 0 ☐**

Interviewer: If childhood perfectionism NOT present, SKIP TO question 15.

If childhood perfectionism is present:

11. Perfectionism Preceded Eating Disorders

- Was perfectionism evident before onset of your eating disorder? Yes ☐ No ☐

12. Age onset of Perfectionism

- How old were you when your perfectionism started? Age: _____

13. Increased Perfectionism

- Has there been an evidence of an increase of perfectionism ever since? Yes ☐ No ☐

If YES to question 13:

14. Age When Perfectionism Increased

- How old were you when your perfectionism increased? Age: _____

Rigidity Domain

Childhood Rigidity

15. Childhood Rule Driven

- Were you the kind of person who felt she always had to follow rules? For example, how far did you bend or break rules that were set by your parents or teachers? Can you give me an example of this?
- How did you feel if you did break a rule? (E.g. guilty, ashamed, would you keep it a secret?)
- Were you rather traditional as a child? In what way? Can you give me an example?

15. Childhood Rule Driven **2** ☐ **1** ☐ **0** ☐

16. Childhood Inflexibility/Stubbornness

- How easy or difficult did you find it adjusting to change? Can you give me an example of this?

Additional Probes:

- What about periods of transition such as moving to a new town, changing schools (e.g. elementary to high school), changes in teacher?
- If there were changes in your parents' lives (e.g. separation, work, living arrangements etc.), how easy did you find it to adjust and accommodate? Can you please give me an example?

- To what extent were you the sort of person who liked to make written plans/notes or have intricate detail about the time ahead e.g. holidays?
- Were you the sort of person who liked to make sure you had contingency plans in mind? For example, did you keep asking "What if"? What would happen if your plans had to be changed (e.g. by others or by circumstances?)
- Could you cope with having to change your plans at short notice? (Can you give me examples?) Would you get angry or irritated?
- How far would you say you liked things to be uncertain or unpredictable? Would you find this exciting or uncomfortable?
- When you made your mind up to do something, would you carry it through no matter what? Can you give me an example about that?
- Did others ever comment about that? What did they say? Did that caused you any problems?

16. Childhood Inflexibility/Stubbornness **2** ☐ **1** ☐ **0** ☐

17. Global Childhood Rigidity

Note: Code item based on questions 3 & 4. Code 2 if either question is coded 2; otherwise code 0.

17. Global Childhood Rigidity **2** ☐ **0** ☐

Impulsive Behaviors

I am going to read you a list of behaviors. I would like you to tell me if you have ever had an episode when you have engaged in these behaviors and experienced a lack of control over them during your lifetime.

If yes:
1. **How old were you when this happened for the first time?**
2. **At what age was this behavior a problem? How often did it happen at worst?** (Record in times per month, if possible.)
3. **At what age did this behavior stop being a problem?** (If problem is ongoing, code as 000)

(Probe for regret after episode; others commenting on behavior or expressing concern; suffering or distress caused by the behavior as indicators of impulsivity/lack of control.)

	Out of Control	Age Onset	Age At Worst	Frequency at Worst (Xs/mo)	Age Offset
1. Binge eating	NO☐ YES☐				
2. Drinking more alcohol than you felt was sensible or more than 38 units a week	NO☐ YES☐				
3. Shoplifting or stealing	NO☐ YES☐				
4. Gambling	NO☐ YES☐				
5. Hitting someone or breaking things	NO☐ YES☐				
6. Provoking a fight or getting in an argument	NO☐ YES☐				
7. Firesetting	NO☐ YES☐				
8. Cutting/burning/hitting/biting etc yourself	NO☐ YES☐				
9. Overdosing	NO☐ YES☐				
10. Taking heroin, LSD amphetamines or street drugs	NO☐ YES☐				
11. Spending more than you felt was sensible	NO☐ YES☐				
12. Involved in sexual activities that could be described as disinhibited or reckless	NO☐ YES☐				

Summary Scoring of Childhood Rigidity and Perfectionism

Item/Scale	Name of Item or Scale	How to score	(0, 1, 2)
1.	General Childhood Perfectionism	Item score	
2.	School Work Perfectionism	Item score	
3.	Self Care Perfectionism	Item score	
4.	Order, Tidiness Perfectionism	Item score	
5.	Pet Perfectionism	Item score	
6	Hobby Perfectionism	Item score	
7.	Other Areas Perfectionism	Item score	
8.	Childhood Order and Symmetry	Items 3 & 4 2 = 2 on either 0 = All other	
9.	Childhood Cautiousness	Item score	
10.	Childhood Excessive Doubt	Item score	
11.	Perfectionism Preceded ED	0=NO; 1=YES	
12.	Age onset of Perfectionism		_____ Years
13.	Increased Perfectionism	0=NO; 1=YES	
14.	Age When Perfectionism Increased		_____ Years
15.	Childhood Rule Driven		
16.	Childhood Inflexibility/Stubbornness	Item score	
17.	Global Childhood Rigidity	Items 15 & 16 2 = 2 on either 0 = All other	

Appendix 1.8: Depression, anxiety and stress scale (DASS).

DASS21

Name: *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Appendix 1.9: Obsessive-compulsive inventory-revised (OCI-R).

The following statements refer to experiences that many people have in their everyday lives.

Circle the number that best describes **HOW MUCH** that experience has **DISTRESSED or BOTHERED you during the PAST MONTH**. The numbers refer to the following verbal labels:

0 = Not at all
1 = A little
2 = Moderately
3 = A lot
4 = Extremely

1.	I have saved up so many things that they get in the way	0	1	2	3	4
2.	I check things more often than necessary.	0	1	2	3	4
3.	I get upset if objects are not arranged properly	0	1	2	3	4
4.	I feel compelled to count while I am doing things.	0	1	2	3	4
5.	I find it difficult to touch an object when I know it has been touched by strangers or certain people.	0	1	2	3	4
6.	I find it difficult to control my own thoughts	0	1	2	3	4
7.	I collect things I don't need.	0	1	2	3	4
8.	I repeatedly check doors, windows, drawers, etc.	0	1	2	3	4
9.	I get upset if others change the way I have arranged things.	0	1	2	3	4
10.	I feel I have to repeat certain numbers.	0	1	2	3	4
11.	I sometimes have to wash or clean myself simply because I feel contaminated	0	1	2	3	4
12.	I am upset by unpleasant thoughts that come into my mind against my will	0	1	2	3	4
13.	I avoid throwing things away because I am afraid I might need them later.	0	1	2	3	4
14.	I repeatedly check gas and water taps and light switches after turning them off.	0	1	2	3	4
15.	I need things to be arranged in a particular order.	0	1	2	3	4
16.	I feel that there are good and bad numbers.	0	1	2	3	4
17.	I wash my hands more often and longer than necessary	0	1	2	3	4
18.	I frequently get nasty thoughts and have difficulty in getting rid of them.	0	1	2	3	4

Please check that you have answered all the questions.

Appendix 1.10: Rosenberg self-esteem scale (RSE).

Below is a list of statements dealing with your general feelings about yourself. Please indicate to what extent you agree with the statement.

3= Strongly agree
2= Agree
1= Disagree
0= Strongly disagree

1. On the whole, I am satisfied with myself.			
Strongly disagree			Strongly agree
0	1	2	3

2. At times, I think I am no good at all.			
Strongly disagree			Strongly agree
0	1	2	3

3. I feel that I have a number of good qualities.			
Strongly disagree			Strongly agree
0	1	2	3

4. I am able to do things as well as most other people.			
Strongly disagree			Strongly agree
0	1	2	3

5. I feel that I do not have much to be proud of.			
Strongly disagree			Strongly agree
0	1	2	3

6. I certainly feel useless at times.			
Strongly disagree			Strongly agree
0	1	2	3

7. I feel that I'm a person of worth, at least on an equal plane with others.			
Strongly disagree			Strongly agree

0 1 2 3

8. I wish I could have more respect for myself.

Strongly disagree Strongly agree

0 1 2 3

9. All in all, I am inclined to feel that I am failure.

Strongly disagree Strongly agree

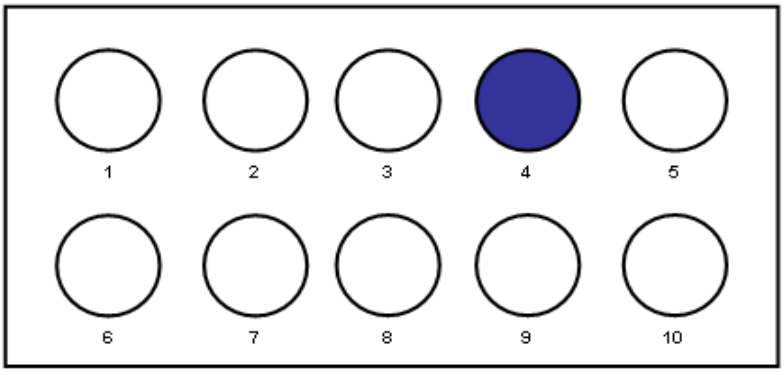
0 1 2 3

10. I take a positive attitude toward myself.

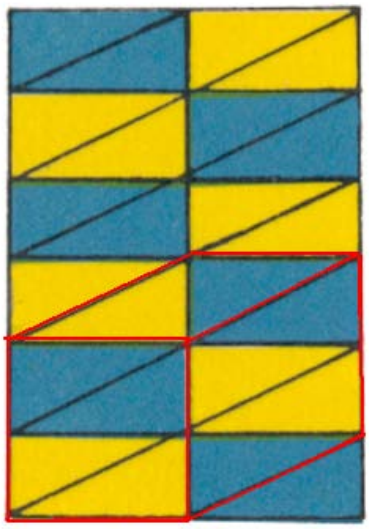
Strongly disagree Strongly agree

0 1 2 3

Appendix 1.11: Brixton task



Appendix 1.12: Group embedded figures task – Target shape and example of a trial



Appendix 1.13: Difficulties in emotion regulation scale (DERS)

DERS

Please indicate how often the following statements apply to you by circling the appropriate number from the sc
below on the line beside each item:

1	2	3	4	5
Almost never (0-10%)	sometimes (11-35%)	about half the time (36-65%)	most of the time (66-90%)	almost always (91-100%)

1) I am clear about my feelings
1 2 3 4 5

2) I pay attention to how I feel
1 2 3 4 5

3) I experience my emotions as overwhelming and out of my control
1 2 3 4 5

4) I have no idea how I am feeling
1 2 3 4 5

5) I have difficulty making sense out of my feelings
1 2 3 4 5

6) I am attentive to my feelings
1 2 3 4 5

7) I know exactly how I am feeling
1 2 3 4 5

8) I care about what I am feeling
1 2 3 4 5

9) I am confused about how I feel
1 2 3 4 5

10) When I'm upset, I acknowledge my emotions
1 2 3 4 5

11) When I'm upset, I become angry with myself for feeling that way
1 2 3 4 5

12) When I'm upset, I become embarrassed for feeling that way
1 2 3 4 5

13) When I'm upset, I have difficulty getting work done
1 2 3 4 5

14) When I'm upset, I become out of control
1 2 3 4 5

15) When I'm upset, I believe that I will remain that way for a long time
1 2 3 4 5

16) When I'm upset, I believe that I'll end up feeling very depressed
1 2 3 4 5

17) When I'm upset, I believe my feelings are valid and important
1 2 3 4 5

18) When I'm upset, I have difficulty focusing on other things
1 2 3 4 5

19) When I'm upset, I feel out of control
1 2 3 4 5

20) When I'm upset, I can still get things done
1 2 3 4 5

21) When I'm upset, I feel ashamed with myself for feeling that way
1 2 3 4 5

22) When I'm upset, I know that I can find a way to eventually feel better
1 2 3 4 5

23) When I'm upset, I feel like I am weak
1 2 3 4 5

24) When I'm upset, I feel like I can remain in control or my behaviours
1 2 3 4 5

25) When I'm upset, I feel guilty for feeling that way
1 2 3 4 5

26) When I'm upset, I have difficulty concentrating
1 2 3 4 5

27) When I'm upset, I have difficulty controlling my behaviours
1 2 3 4 5

28) When I'm upset, I believe that there is nothing I can do to make myself feel better
1 2 3 4 5

29) When I'm upset, I become irritated with myself for feeling that way
1 2 3 4 5

30) When I'm upset, I start to feel very bad about myself
1 2 3 4 5

31) When I'm upset, I believe that wallowing in it is all I can do
1 2 3 4 5

32) When I'm upset, I lose control over my behaviours
1 2 3 4 5

33) When I'm upset, I have difficulty thinking about anything else
1 2 3 4 5

34) When I'm upset, I take time to figure out what I'm really feeling
1 2 3 4 5

35) When I'm upset, it takes me a long time to feel better
1 2 3 4 5

36) When I'm upset, my emotions feel overwhelming
1 2 3 4 5

Appendix 1.14: Behavioural inhibition and behavioural activation scale (BIS/BAS)

BIS/BAS

Name_____ **Date**_____

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Choose only *one* response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. We would encourage you to please respond to all the items, as blank responses will impact the validity of the questionnaire. Thank you.

Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

Please circle your chosen response.

		Very true for me	Somewhat true for me	Somewhat false for me	Very false for me
1	A person's family is the most important thing in life	1	2	3	4
2	Even if something bad is about to happen to me, I rarely experience fear or nervousness	1	2	3	4
3	I go out of my way to get things I want	1	2	3	4
4	When I'm doing well at something I love to keep at it	1	2	3	4
5	I'm always willing to try something new if I think it will be fun	1	2	3	4
6	How I dress is important to me	1	2	3	4
7	When I get something I want, I feel excited and energized	1	2	3	4
8	Criticism or scolding hurts me quite a bit	1	2	3	4
9	When I want something I usually go all-out to get it	1	2	3	4
10	I will often do things for no other reason than that they might be fun	1	2	3	4
11	It's hard for me to find the time to do things such as get a haircut	1	2	3	4
12	If I see a chance to get something I want I move on it right away	1	2	3	4

13	I feel pretty worried or upset when I think or know somebody is angry at me	1	2	3	4
14	When I see an opportunity for something I like I get excited right away	1	2	3	4
15	I often act on the spur of the moment	1	2	3	4
16	If I think something unpleasant is going to happen I usually get pretty “worked up”	1	2	3	4
17	I often wonder why people act the way they do	1	2	3	4
18	When good things happen to me, it affects me strongly	1	2	3	4
19	I feel worried when I think I have done poorly at something important	1	2	3	4
20	I crave excitement and new sensations	1	2	3	4
21	When I go after something I use a “no holds barred” approach	1	2	3	4
22	I have very few fears compared to my friends	1	2	3	4
23	It would excite me to win a contest	1	2	3	4
24	I worry about making mistakes	1	2	3	4

Appendix 1.15: Appetitive motivation scale (AMS)

AMS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do *not* leave any blank. Choose only *one* response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = Strongly disagree
2 = Disagree somewhat
3 = Agree somewhat
4 = Strongly agree

Please circle your chosen response.

		Strongly disagree	Disagree somewhat	Agree somewhat	Strongly agree
1	I like to do things which are new and different	1	2	3	4
2	I like to do things spontaneously	1	2	3	4
3	I tend to do several things all at the same time	1	2	3	4
4	I actively look for new experiences	1	2	3	4
5	I have a feel for how things work	1	2	3	4
6	I look for new sensations	1	2	3	4
7	I am excited by what is new in my field	1	2	3	4
8	I often have lots of spontaneous ideas	1	2	3	4
9	I like to be rewarded for what I do	1	2	3	4
10	I have new ideas all the time	1	2	3	4
11	I enjoy starting projects	1	2	3	4

Appendix 1.16: Reading the mind in the eyes task – examples of stimuli

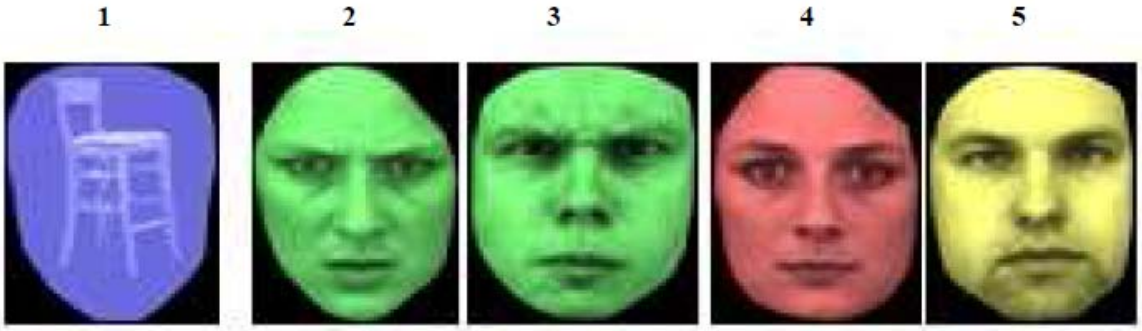
irritated sarcastic

worried friendly

aghast fantasizing

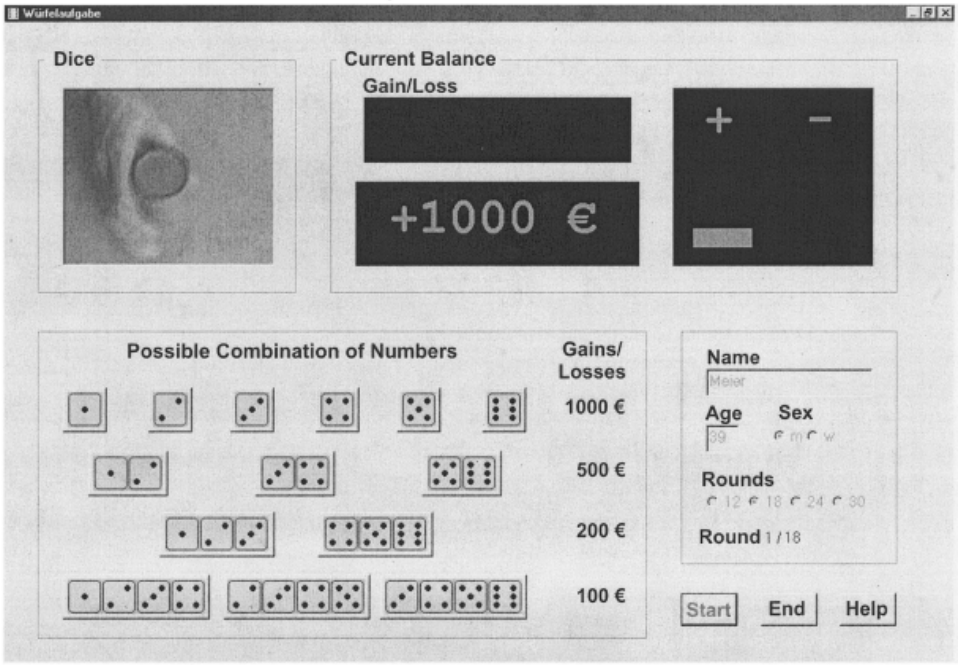
impatient alarmed

Appendix 1.17: Pictorial emotional stroop task – examples of stimuli

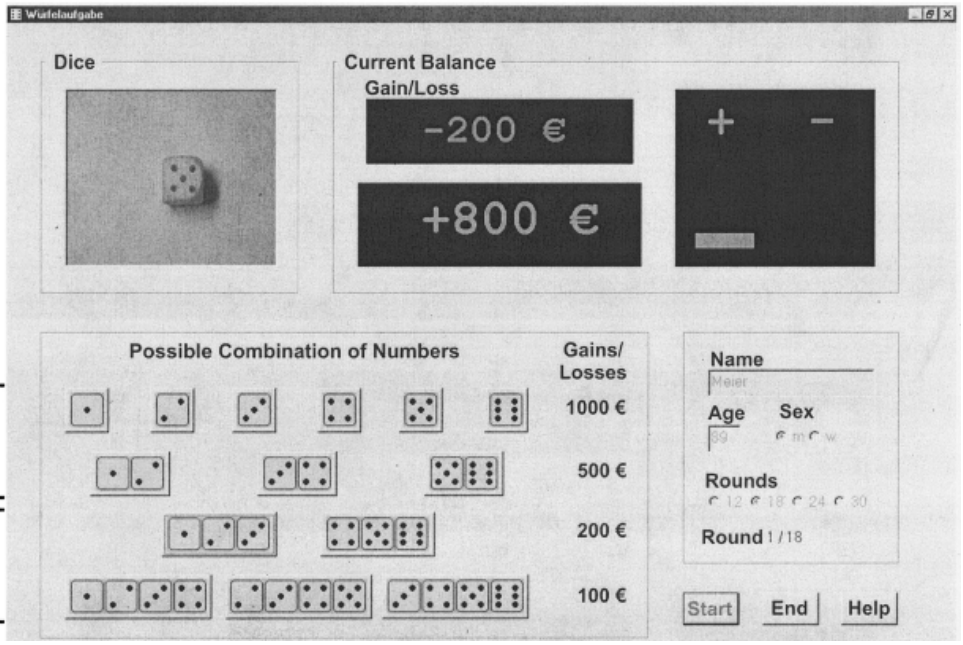


Appendix 1.18: Game of dice task

A



B



Appendix 1.19: Confirmation of ethics approval

The Joint South London and Maudsley and The Institute of Psychiatry NHS Research Ethics Committee
South London REC Office (2)
1st Floor, Camberwell Building
94 Denmark Hill
London
SE5 9RS

Telephone: 020 3299 5033
Facsimile: 020 3299 5085

17 November 2009

Professor Janet Treasure
Director of ED Service, Professor of Psychiatry
Guy's and St Thomas, SLAM NHS Trusts
Dept Academic Psychiatry
Bermondsey Wing
Guy's Hospital
SE1 9RT

Dear Professor Treasure

Study Title:	**Neuropsychological endophenotypes, genes and biomarkers related to eating disorders in twin, family and singleton populations.**
REC reference number:	**09/H0807/67**

Thank you for your letter of 03 November 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by the chair of the Committee on 17 November 2009.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
REC application	2.3	19 August 2009
Investigator CV	Janet L Treasure	
Investigator CV	Frederique Van den Eynde	
Investigator CV	Mrs Amy Karol Harrison	
Investigator CV	Sietske Helder	
Investigator CV	Lot Sternheim	
Protocol		19 August 2009
Protocol flowchart		18 August 2009
Funding Letter	Welcome	29 May 2009
Advertisement	www.eatingresearch.com	18 August 2009
Advertisement	!!!!!!!!!	18 August 2009
Advertisement	Circular e-mail	18 August 2009
Advertisement	Do you have a twin or sister?	18 August 2009
Participant Information Sheet: Carer		18 August 2009
Participant Information Sheet: Patient		18 August 2009
Participant Information Sheet: Control		18 August 2009
Participant Consent Form: Carer		18 August 2009

Participant Consent Form: Control -longer question at 2.		18 August 2009
Participant Consent Form: Control		18 August 2009
Letter of invitation to participant		18 August 2009
Questionnaire: EATATELIFE PHENOTYPE		
Questionnaire: EATATE LIFETIME INTERVIEW		
Questionnaire: SCID Screening Module		
Questionnaire: SCID (for DSM-IV)		
Questionnaire: EDE-Q		18 August 2009
Questionnaire: YBC-EDS Symptoms Checklist		
Questionnaire: Y-BOCS Symptoms Checklist		
Questionnaire: Autism Spectrum Quotent		18 August 2009
Questionnaire: EDDS (lifetime)		18 August 2009
Questionnaire: BIS/BAS		18 August 2009
Questionnaire: DASS21		18 August 2009
Questionnaire: OCI-R		18 August 2009
Questionnaire: EDI-3 RF		18 August 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0807/67	**Please quote this number on all correspondence**

Yours sincerely

Mr T Eaton
Chair

Email: faye.cuffie@nhs.net

Copy to: *Jenny Liebscher, R&D Office*

76, 092 words (excluding references and appendices)